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     (FILE 'HOME' ENTERED AT 23:07:59 ON 13 AUG 2003)

     FILE 'REGISTRY' ENTERED AT 23:08:10 ON 13 AUG 2003
L1            0 S US20020119987/PN
L2            0 S US200200119987/PN
L3            0 S US2002/00119987/PN
L4            0 S US2002-00119987/PN

     FILE 'CAPLUS' ENTERED AT 23:10:00 ON 13 AUG 2003
                E KANG Y/AU
                E KANG YUHONG/AU
L5            1 S E15
                SELECT L5 1 RN

     FILE 'REGISTRY' ENTERED AT 23:11:06 ON 13 AUG 2003
L6            1 S E25
L7            1 S E26
L8            1 S E27
L9            1 S E28
L10           1 S E29
L11           1 S E30
L12           1 S E31
L13           1 S E32
L14           1 S E33
L15           1 S E34
L16           1 S E35
L17           1 S E36
L18           1 S E37
L19           1 S E38
L20           1 S E39
L21           1 S E40
L22           1 S E41
L23           1 S E42
L24           1 S E43
L25           1 S E44
L26           1 S E45
L27           1 S E46
L28           1 S E47

     FILE 'CAPLUS, USPATFULL' ENTERED AT 23:14:05 ON 13 AUG 2003
L29       11298 FILE CAPLUS
L30         438 FILE USPATFULL
     TOTAL FOR ALL FILES
L31       11736 S TETRODOTOXIN OR ANHYDROTETRODOTOXIN OR TETRDAMINOTOXIN OR MET
L32        2862 FILE CAPLUS
L33          66 FILE USPATFULL
     TOTAL FOR ALL FILES
L34        2928 S L9 OR L12 OR L13 OR L14 OR L25 OR L26 OR L27 OR L28
L35       11945 FILE CAPLUS
L36         452 FILE USPATFULL
     TOTAL FOR ALL FILES
L37       12397 S L34 OR L31
L38         153 FILE CAPLUS
L39         219 FILE USPATFULL
     TOTAL FOR ALL FILES
L40         372 S L37 AND PAIN?
L41           0 FILE CAPLUS
L42           0 FILE USPATFULL
     TOTAL FOR ALL FILES
L43           0 S L37 AND SUNERG?
L44           0 FILE CAPLUS
L45           0 FILE USPATFULL
     TOTAL FOR ALL FILES
```

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L46           0 S L37 AND SYERG?
L47          75 FILE CAPLUS
L48          77 FILE USPATFULL
     TOTAL FOR ALL FILES
L49         152 S L37 AND SYNERG?
L50           4 FILE CAPLUS
L51          14 FILE USPATFULL
     TOTAL FOR ALL FILES
L52          18 S L49 AND OPIOID?

     FILE 'REGISTRY' ENTERED AT 23:21:04 ON 13 AUG 2003
L53           1 S 84057-84-1/RN
                SET NOTICE 1 DISPLAY
                SET NOTICE LOGIN DISPLAY

     FILE 'CAPLUS, USPATFULL' ENTERED AT 23:21:31 ON 13 AUG 2003
L54         458 FILE CAPLUS
L55         599 FILE CAPLUS
L56         600 FILE CAPLUS
L57          69 FILE CAPLUS
L58          17 FILE CAPLUS
L59           0 FILE CAPLUS
L60           0 FILE CAPLUS
L61          14 FILE CAPLUS
L62          12 FILE CAPLUS
L63           0 FILE CAPLUS
L64           2 FILE CAPLUS
L65       44755 FILE CAPLUS
L66        8747 FILE USPATFULL
     TOTAL FOR ALL FILES
L67       53502 S MORPHINE OR CODEINE OR METHADONE OR FENTANYL
L68         189 FILE CAPLUS
L69          69 FILE USPATFULL
     TOTAL FOR ALL FILES
L70         258 S L67 AND L37
L71           1 FILE CAPLUS
L72          13 FILE USPATFULL
     TOTAL FOR ALL FILES
L73          14 S L70 AND SYNERG? AND PAIN
L74         166 FILE CAPLUS
L75           3 FILE USPATFULL
     TOTAL FOR ALL FILES
L76         169 S L67 (3S) L37
L77           9 FILE CAPLUS
L78           3 FILE USPATFULL
     TOTAL FOR ALL FILES
L79          12 S L76 AND PAIN
L80           1 FILE CAPLUS
L81           1 FILE USPATFULL
     TOTAL FOR ALL FILES
L82           2 S L79 AND SYNERG?
L83           8 FILE CAPLUS
L84           2 FILE USPATFULL
     TOTAL FOR ALL FILES
L85          10 S L79 NOT L82
                SAVE ALL L10062483/L
L86           2 FILE CAPLUS
L87           1 FILE USPATFULL
     TOTAL FOR ALL FILES
L88           3 S L76 AND SYNERG?
L89           2 FILE CAPLUS
L90           1 FILE USPATFULL
     TOTAL FOR ALL FILES
L91           3 S L88 NOT L84
```

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=> s l49 and (l37 (1s) combin?) and (opioid? or opiate? or l67)
L92           1 FILE CAPLUS
L93           3 FILE USPATFULL

TOTAL FOR ALL FILES
L94           4 L49 AND (L37 (1S) COMBIN?) AND (OPIOID? OR OPIATE? OR L67)

=> s l94 not l91
L95           0 FILE CAPLUS
L96           2 FILE USPATFULL

TOTAL FOR ALL FILES
L97           2 L94 NOT L91

=> d 1-2 hit, ibib

=> s  (l37 (1s) combin?) (1s) (opioid? or opiate? or l67)
L98           5 FILE CAPLUS
L99           1 FILE USPATFULL

TOTAL FOR ALL FILES
L100          6 (L37 (1S) COMBIN?) (1S) (OPIOID? OR OPIATE? OR L67)

=> d 1-5 all
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     FILE 'REGISTRY' ENTERED AT 23:08:10 ON 13 AUG 2003
L1             0 S US20020119987/PN
L2             0 S US200200119987/PN
L3             0 S US2002/00119987/PN
L4             0 S US2002-00119987/PN

     FILE 'CAPLUS' ENTERED AT 23:10:00 ON 13 AUG 2003
                 E KANG Y/AU
                 E KANG YUHONG/AU
L5             1 S E15
                 SELECT L5 1 RN

     FILE 'REGISTRY' ENTERED AT 23:11:06 ON 13 AUG 2003
L6             1 S E25
L7             1 S E26
L8             1 S E27
L9             1 S E28
L10            1 S E29
L11            1 S E30
L12            1 S E31
L13            1 S E32
L14            1 S E33
L15            1 S E34
L16            1 S E35
L17            1 S E36
L18            1 S E37
L19            1 S E38
L20            1 S E39
L21            1 S E40
L22            1 S E41
L23            1 S E42
L24            1 S E43
L25            1 S E44
L26            1 S E45
L27            1 S E46
L28            1 S E47

     FILE 'CAPLUS, USPATFULL' ENTERED AT 23:14:05 ON 13 AUG 2003
L29        11298 FILE CAPLUS
L30          438 FILE USPATFULL
     TOTAL FOR ALL FILES
L31        11736 S TETRODOTOXIN OR ANHYDROTETRODOTOXIN OR TETRDAMINOTOXIN OR MET
L32         2862 FILE CAPLUS
L33           66 FILE USPATFULL
     TOTAL FOR ALL FILES
L34         2928 S L9 OR L12 OR L13 OR L14 OR L25 OR L26 OR L27 OR L28
L35        11945 FILE CAPLUS
L36          452 FILE USPATFULL
     TOTAL FOR ALL FILES
L37        12397 S L34 OR L31
L38          153 FILE CAPLUS
L39          219 FILE USPATFULL
     TOTAL FOR ALL FILES
L40          372 S L37 AND PAIN?
L41            0 FILE CAPLUS
L42            0 FILE USPATFULL
     TOTAL FOR ALL FILES
L43            0 S L37 AND SUNERG?
L44            0 FILE CAPLUS
L45            0 FILE USPATFULL
     TOTAL FOR ALL FILES
L46            0 S L37 AND SYERG?
L47           75 FILE CAPLUS
```

```
L48           77 FILE USPATFULL
     TOTAL FOR ALL FILES
L49          152 S L37 AND SYNERG?
L50            4 FILE CAPLUS
L51           14 FILE USPATFULL
     TOTAL FOR ALL FILES
L52           18 S L49 AND OPIOID?

     FILE 'REGISTRY' ENTERED AT 23:21:04 ON 13 AUG 2003
L53            1 S 84057-84-1/RN
                 SET NOTICE 1 DISPLAY
                 SET NOTICE LOGIN DISPLAY

     FILE 'CAPLUS, USPATFULL' ENTERED AT 23:21:31 ON 13 AUG 2003
L54          458 FILE CAPLUS
L55          599 FILE CAPLUS
L56          600 FILE CAPLUS
L57           69 FILE CAPLUS
L58           17 FILE CAPLUS
L59            0 FILE CAPLUS
L60            0 FILE CAPLUS
L61           14 FILE CAPLUS
L62           12 FILE CAPLUS
L63            0 FILE CAPLUS
L64            2 FILE CAPLUS
L65        44755 FILE CAPLUS
L66         8747 FILE USPATFULL
     TOTAL FOR ALL FILES
L67        53502 S MORPHINE OR CODEINE OR METHADONE OR FENTANYL
L68          189 FILE CAPLUS
L69           69 FILE USPATFULL
     TOTAL FOR ALL FILES
L70          258 S L67 AND L37
L71            1 FILE CAPLUS
L72           13 FILE USPATFULL
     TOTAL FOR ALL FILES
L73           14 S L70 AND SYNERG? AND PAIN
L74          166 FILE CAPLUS
L75            3 FILE USPATFULL
     TOTAL FOR ALL FILES
L76          169 S L67 (3S) L37
L77            9 FILE CAPLUS
L78            3 FILE USPATFULL
     TOTAL FOR ALL FILES
L79           12 S L76 AND PAIN
L80            1 FILE CAPLUS
L81            1 FILE USPATFULL
     TOTAL FOR ALL FILES
L82            2 S L79 AND SYNERG?
L83            8 FILE CAPLUS
L84            2 FILE USPATFULL
     TOTAL FOR ALL FILES
L85           10 S L79 NOT L82

=> save all
ENTER NAME OR (END):l10062483/l
L# LIST L1-L85 HAS BEEN SAVED AS 'L10062483/L'
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L52 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:296286 CAPLUS
DN 133:27071
TI **Synergistically** interacting dopamine D1 and NMDA receptors mediate nonvesicular transporter-dependent GABA release from rat striatal medium spiny neurons
AU Schoffelmeer, Anton N. M.; Vanderschuren, Louk J. M. J.; De Vries, Taco J.; Hogenboom, Francois; Wardeh, George; Mulder, Arie H.
CS Research Institute Neurosciences Vrije Universiteit, Department of Pharmacology, Medical Faculty, Free University, Amsterdam, 1081 BT, Neth.
SO Journal of Neuroscience (2000), 20(9), 3496-3503
CODEN: JNRSDS; ISSN: 0270-6474
PB Society for Neuroscience
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB Given the complex interactions between dopamine D1 and glutamate NMDA receptors in the striatum, we investigated the role of these receptors in transporter-mediated GABA release from cultured medium spiny neurons of rat striatum. Like NMDA receptor-mediated [3H]-GABA release, that induced by prolonged (20 min) dopamine D1 receptor activation was enhanced on omission of external calcium, was action potential-independent (**tetrodotoxin**-insensitive), and was diminished by the GABA transporter blocker nipecotic acid, indicating the involvement of transporter-mediated release. Interestingly, lowering the external sodium concn. only reduced the stimulatory effect of NMDA. Blockade of Na+/K+-ATPase by ouabain enhanced NMDA-induced but abolished dopamine-induced release. Moreover, dopamine appeared to potentiate the effect of NMDA on [3H]-GABA release. These effects of dopamine were mimicked by forskolin. .mu.-**Opioid** receptor-mediated inhibition of adenylyl cyclase by morphine reduced dopamine- and NMDA-induced release. These results confirm previous studies indicating that NMDA receptor activation causes a slow action potential-independent efflux of GABA by reversal of the sodium-dependent GABA transporter on sodium entry through the NMDA receptor channel. Moreover, our data indicate that activation of G-protein-coupled dopamine D1 receptors also induces a transporter-mediated increase in spontaneous GABA release, but through a different mechanism of action, i.e., through cAMP-dependent inhibition of Na+/K+-ATPase, inducing accumulation of intracellular sodium, reversal of the GABA carrier, and potentiation of NMDA-induced release. These receptor interactions may play a crucial role in the behavioral activating effects of psychostimulant drugs.
ST dopamine D1 NMDA receptor transporter dependent GABA release striatum
IT Dopamine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D1; **synergistically** interacting dopamine D1 and NMDA receptors mediate nonvesicular transporter-dependent GABA release from rat striatal medium spiny neurons)
IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GABA transporter; **synergistically** interacting dopamine D1 and NMDA receptors mediate nonvesicular transporter-dependent GABA release from rat striatal medium spiny neurons)
IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NMDA-binding; **synergistically** interacting dopamine D1 and NMDA receptors mediate nonvesicular transporter-dependent GABA release from rat striatal medium spiny neurons)
IT Brain
(corpus striatum; **synergistically** interacting dopamine D1 and NMDA receptors mediate nonvesicular transporter-dependent GABA release

from rat striatal medium spiny neurons)

IT Biological transport
(sodium; NMDA receptor activation causes a slow action potential-independent efflux of GABA from rat striatal medium spiny neurons by reversal of the sodium-dependent GABA transporter on sodium entry through the NMDA receptor channel)

IT **Opioid** receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.mu.-**opioid**; D1 and .mu.-**opioid** receptors regulate transporter-dependent GABA release from rat striatal medium spiny neurons in a cAMP-dependent manner)

IT 60-92-4, CAMP
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(D1 and .mu.-**opioid** receptors regulate transporter-dependent GABA release from rat striatal medium spiny neurons in a cAMP-dependent manner)

IT 7440-23-5, Sodium, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NMDA receptor activation causes a slow action potential-independent efflux of GABA from rat striatal medium spiny neurons by reversal of the sodium-dependent GABA transporter on sodium entry through the NMDA receptor channel)

IT 9000-83-3
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(potassium-sodium-dependent; NMDA receptor activation causes a slow action potential-independent efflux of GABA from rat striatal medium spiny neurons by reversal of the sodium-dependent GABA transporter on sodium entry)

IT 6384-92-5, NMDA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**synergistically** interacting dopamine D1 and NMDA receptors mediate nonvesicular transporter-dependent GABA release from rat striatal medium spiny neurons)

IT 56-12-2, GABA, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**synergistically** interacting dopamine D1 and NMDA receptors mediate nonvesicular transporter-dependent GABA release from rat striatal medium spiny neurons)

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Albin, R; Trends Neurosci 1989, V12, P366 MEDLINE
(2) Attwell, D; Neuron 1993, V11, P401 CAPLUS
(3) Beckman, M; J Neurosci 1998, V18, P6103 CAPLUS
(4) Belhage, B; Neuroscience 1993, V54, P1019 CAPLUS
(5) Bernath, S; Neuroscience 1990, V36, P677 CAPLUS
(6) Bernstein, E; J Biol Chem 1999, V274, P889 CAPLUS
(7) Bertorello, A; Nature 1990, V347, P386 CAPLUS
(8) Blank, T; Proc Natl Acad Sci USA 1997, V94, P14859 CAPLUS
(9) Blaustein, M; Ann NY Acad Sci USA 1991, V639, P254 CAPLUS
(10) Bockaert, J; J Physiol (Paris) 1986, V81, P219 MEDLINE
(11) Breukel, A; Eur J Neurosci 1998, V10, P106 MEDLINE
(12) Cepeda, C; Dev Neurosci 1998, V20, P1 CAPLUS
(13) Chergui, K; Neuropharmacology 1999, V38, P223 CAPLUS
(14) Del Arco, A; Neuropharmacology 1998, V37, P199 CAPLUS
(15) Di Chiara, G; Trends Neurosci 1994, V17, P228 CAPLUS

(16) Duarte, C; Brain Res 1993, V611, P130 CAPLUS
(17) Dunlop, J; J Neurochem 1991, V57, P1388 CAPLUS
(18) Erecinska, M; Biochem Pharmacol 1987, V36, P3547 CAPLUS
(19) Fienberg, A; Science 1998, V281, P838 CAPLUS
(20) Groves, P; Brain Res Rev 1983, V5, P109
(21) Jaffe, E; P R Health Sci J 1988, V7, P99 MEDLINE
(22) Kalivas, P; Curr Opin Neurobiol 1999, V9, P223 CAPLUS
(23) Kelley, A; Psychobiology 1999, V27, P198
(24) Knable, M; J Psychopharmacol 1997, V11, P123 CAPLUS
(25) Koob, G; Science 1997, V278, P52 CAPLUS
(26) Kuczenski, R; J Neurosci 1989, V9, P2051 CAPLUS
(27) Malva, J; Br J Pharmacol 1994, V113, P1439 CAPLUS
(28) Maycox, P; Trends Neurosci 1990, V13, P83 CAPLUS
(29) Nicola, S; J Neurosci 1996, V16, P1591 CAPLUS
(30) Nishi, A; J Neurochem 1999, V73, P1492 CAPLUS
(31) Pierce, R; Brain Res Rev 1997, V25, P192 CAPLUS
(32) Reid, M; Synapse 1997, V27, P95 CAPLUS
(33) Robbins, T; Curr Opin Neurobiol 1996, V6, P228 CAPLUS
(34) Schiffmann, S; J Physiol (Lond) 1995, V483, P95 CAPLUS
(35) Schoffelmeer, A; Eur J Pharmacol 1988, V154, P169 CAPLUS
(36) Schoffelmeer, A; Synapse 1997, V25, P381 CAPLUS
(37) Sihra, T; J Neurochem 1987, V49, P261 CAPLUS
(38) Smith, A; Trends Neurosci 1990, V13, P259 CAPLUS
(39) Snyder, G; J Neurosci 1998, V18, P10297 CAPLUS
(40) Surmeier, D; Neuron 1995, V14, P385 CAPLUS
(41) Surmeier, D; Proc Natl Acad Sci USA 1992, V89, P10178 CAPLUS
(42) Tian, Y; Neurosci Lett 1994, V173, P143 CAPLUS
(43) Van Vliet, B; Eur J Pharmacol Mol Pharmacol 1991, V208, P105 CAPLUS
(44) Wang, J; J Neurochem 1992, V58, P204 CAPLUS
(45) Weiss, S; J Neurochem 1988, V51, P435 CAPLUS
(46) White, F; J Pharmacol Exp Ther 1993, V66, P1075
(47) Xue, C; J Neurochem 1996, V67, P352 CAPLUS
(48) Zhang, X; J Neurosci 1998, V18, P488 CAPLUS

L52 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:351162 CAPLUS
DN 133:790
TI New use of glutamate antagonists for the treatment of cancer
IN Ikonomidou, Hrissanthi
PA Germany
SO Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K031-435
ICS A61K031-55; A61K031-495
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1002535	A1	20000524	EP 1998-250380	19981028
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AU 9964750	A1	20000515	AU 1999-64750	19991022
	EP 1124553	A1	20010822	EP 1999-952622	19991022
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002528415	T2	20020903	JP 2000-578005	19991022
PRAI	EP 1998-250380	A	19981028		
	WO 1999-EP8004	W	19991022		

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of cancer. Inhibitors of the interaction of glutamate with the AMPA, kainate, or NMDA receptor complexes are likely to be useful in treating cancer and can be formulated as pharmaceutical compns. They can be identified by appropriate screens.
ST AMPA receptor glutamate interaction inhibition antitumor; kainate receptor glutamate interaction inhibition antitumor; NMDA receptor glutamate interaction inhibition antitumor; glutamate antagonist cancer treatment; antitumor screening glutamate antagonist cancer treatment
IT Ion channel blockers
(AMPA receptor channel blockers; glutamate antagonists for cancer treatment)
IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(AMPA-binding; glutamate antagonists for cancer treatment)
IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Joro spider and others; glutamate antagonists for cancer treatment)
IT Glutamate antagonists
(NMDA antagonists; glutamate antagonists for cancer treatment)
IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NMDA-binding; glutamate antagonists for cancer treatment)
IT Spider
(NSTX spider toxin; glutamate antagonists for cancer treatment)
IT Intercalation
(agents; glutamate antagonists for cancer treatment, and combinations with other agents)
IT Amino acids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(alkanoic; glutamate antagonists for cancer treatment)

IT Nutrients
(anti-; glutamate antagonists for cancer treatment, and combinations with other agents)

IT Amines, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arom., diarylalkylamines; glutamate antagonists for cancer treatment)

IT Cycloalkanes
Cycloalkanes
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bicyclic, benzobicycloalkanes; glutamate antagonists for cancer treatment)

IT Hydroxamic acids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cyclic amino hydroxamates; glutamate antagonists for cancer treatment)

IT Bicyclic compounds
Bicyclic compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cycloalkanes, benzobicycloalkanes; glutamate antagonists for cancer treatment)

IT Amides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; glutamate antagonists for cancer treatment)

IT Amines, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diamines, with .sigma.-receptor affinity; glutamate antagonists for cancer treatment)

IT Venoms
(diarylalkylamines related to; glutamate antagonists for cancer treatment)

IT Antitumor agents
Drug delivery systems
Drug screening
Glutamate antagonists
(glutamate antagonists for cancer treatment)

IT Antibodies
Heterocyclic compounds
Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for cancer treatment)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glutamate antagonists for cancer treatment)

IT Alkylating agents, biological
Cytotoxic agents
Gene therapy
Hyperthermia (therapeutic)
Immunomodulators
Radiotherapy
(glutamate antagonists for cancer treatment, and combinations with other agents)

IT Antisense oligonucleotides
Corticosteroids, biological studies
Interferons
Interleukin 1
Interleukin 7
Interleukins
Natural products, pharmaceutical
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for cancer treatment, and combinations with other agents)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutamate-transporting, activators; glutamate antagonists for cancer treatment)

IT Alcohols, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heterocyclic; glutamate antagonists for cancer treatment)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(kainate-binding; glutamate antagonists for cancer treatment)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; glutamate antagonists for cancer treatment)

IT Nerve, neoplasm
Nerve, neoplasm
(neuroblastoma, inhibitors; glutamate antagonists for cancer treatment)

IT Antitumor agents
(neuroblastoma; glutamate antagonists for cancer treatment)

IT Heterocyclic compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrogen, benzo-fused azacyclic compds.; glutamate antagonists for cancer treatment)

IT Amines, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamines, nonpolymeric; glutamate antagonists for cancer treatment)

IT Proliferation inhibition
(proliferation inhibitors; glutamate antagonists for cancer treatment, and combinations with other agents)

IT Radionuclides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiolabeled quinoxalinedione derivs.; glutamate antagonists for cancer treatment)

IT Amides, biological studies
Amides, biological studies
Sulfates, biological studies
Sulfates, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulfamates, derivs.; glutamate antagonists for cancer treatment)

IT Drug interactions

(**synergistic**; glutamate antagonists for cancer treatment, and combinations with other agents)

IT Amines, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tetracyclic amine derivs.; glutamate antagonists for cancer treatment)

IT Nephila clavata
(toxin; glutamate antagonists for cancer treatment)

IT Vaccines
Vaccines
(tumor; glutamate antagonists for cancer treatment, and combinations with other agents)

IT Biological transport
(uptake, glutamate uptake accelerators; glutamate antagonists for cancer treatment)

IT Antitumor agents
Antitumor agents
(vaccines; glutamate antagonists for cancer treatment, and combinations with other agents)

IT Wasp
(venom, toxins; glutamate antagonists for cancer treatment)

IT **Opioid** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.sigma.-**opioid**, diamines with affinity for; glutamate antagonists for cancer treatment)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; glutamate antagonists for cancer treatment, and combinations with other agents)

IT Ketones, biological studies
Oximes
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-; glutamate antagonists for cancer treatment)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.; glutamate antagonists for cancer treatment, and combinations with other agents)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.; glutamate antagonists for cancer treatment, and combinations with other agents)

IT 134234-13-2, CP 101581
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CP 101581; glutamate antagonists for cancer treatment)

IT 56-40-6, Glycine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA/glycine/polyamine receptor/ion channel complex; glutamate antagonists for cancer treatment)

IT 74-79-3D, L-Arginine, derivs., biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO biosynthesis inhibitor; glutamate antagonists for cancer treatment)

IT 170142-29-7, ZD 9379
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ZD 9379; glutamate antagonists for cancer treatment)

IT 161605-73-8, ZK 200775
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ZK 200775; glutamate antagonists for cancer treatment)

IT 59-30-3, Folic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antifolates; glutamate antagonists for cancer treatment, and combinations with other agents)

IT 270-68-8D, Isoindole, spiro derivs. 607-28-3D, Indole-2,3-dione-3-oxime, derivs. 11095-43-5D, Benzothiophene, derivs. 16502-01-5D, derivs. 270902-40-4D, aryl derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arginine-derived NO biosynthesis inhibitor; glutamate antagonists for cancer treatment)

IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(arginine-derived NO biosynthesis inhibitor; glutamate antagonists for cancer treatment)

IT 50-47-5, Desipramine 51-17-2D, Benzimidazole, derivs. 54-05-7, Chloroquine 56-22-4, TE 393 56-40-6D, Aminoethanoic acid, derivs. 56-54-2, Chinidin 56-86-0D, L-Glutamic acid, derivs., biological studies 57-41-0, Diphenylhydantoin 59-31-4D, 2(1H)-Quinolone, derivs. 63-91-2D, L-Phenylalanine, derivs., biological studies 68-41-7, D-Cycloserine 71-44-3D, Spermine, N-3-phenylpropionyl derivs. 73-22-3D, L-Tryptophan, derivs., biological studies 75-04-7D, Ethylamine, derivs. 75-19-4D, Cyclopropane, derivs. 77-10-1, Phencyclidine 77-10-1D, Phencyclidine, derivs. 77-37-2, Procyclidine 83-74-9, Ibogaine 83-89-6, Quinacrine 86-42-0, Amodiaquine 86-74-8D, Carbazole, derivs. 86-95-3D, derivs. 86-96-4D, Quinazoline-2,4-dione, derivs. 91-19-0D, Quinoxaline, arylthio derivs. 91-19-0D, Quinoxaline, derivs. 91-19-0D, Quinoxaline, fused cycloalkyl and dione derivs. 91-20-3D, Naphthalene, Ph derivs., biological studies 91-21-4D, derivs. 91-22-5D, Quinoline, derivs., biological studies 91-56-5D, Isatine, derivs. 91-64-5D, 2H-1-Benzopyran-2-one, derivs. 93-10-7D, Quinoline-2-carboxylic acid, derivs. 97-77-8, Disulfiram 98-98-6D, Pyridine-2-carboxylic acid, derivs. 108-91-8D, Cyclohexylamine, aryl derivs. 108-95-2D, Phenol, derivs., biological studies 110-60-1, Putrescine 110-85-0D, Piperazine, derivs., biological studies 110-86-1D, Pyridine, derivs., biological studies 110-89-4D, Piperidine, derivs., biological studies 113-00-8D, Guanidine, derivs. 113-79-1, Arginine vasopressin 120-72-9D, Indole, derivs. 124-20-9, Spermidine 125-71-3, Dextromethorphan 125-73-5 130-95-0, Chinine 141-43-5D, 2-Hydroxy-ethylamine, derivs. 153-94-6D, D-Tryptophan, derivs. 244-70-2D, 1H-Pyrido[4,3-b]indole, derivs. 253-52-1D, Phthalazine, derivs. 253-82-7D, Quinazoline, derivs. 255-18-5D, 2H-1,2,4-Benzothiadiazine, derivs. 256-81-5D, 5H-Dibenzo[a,d]cycloheptene, derivs. 264-19-7D, 1H-2-Benzazepine, derivs. 264-23-3D, 1H-2,3-Benzodiazepine, derivs. 281-23-2D, Adamantane, derivs. 288-14-2D, Isoxazole, derivs. 290-37-9D, Pyrazine, derivs. 292-64-8D, Cyclooctane, imine derivs. 302-01-2D, Hydrazine, .beta.-hydrazine phosphonates, biological studies 312-84-5, D-Serine 359-85-3D, derivs. 469-62-5, Dextropropoxyphene 487-79-6D, Kainic acid, derivs. 492-27-3, Kynurenic acid 492-27-3D, Kynurenic acid, derivs. 493-08-3D, Chroman, derivs. 496-93-5, L-Canaline 503-83-3D, derivs. 504-73-4D, 2-Isoxazoline, derivs. 507-09-5D, Thioacetic acid, 3-indolyl derivs. 548-93-6D, 3-Hydroxyanthranilic acid, derivs. 575-19-9D, derivs. 616-45-5D, Pyrrolidone, derivs. 635-46-1D, 1,2,3,4-Tetrahydroquinoline,

derivs. 635-51-8, Phenylsuccinic acid 760-78-1, Norvaline 768-94-5, Amantadine 833-48-7D, Suberane, spiro derivs. 1003-51-6, HA 966 1115-90-8 1116-22-9 1196-57-2D, 2(1H)-Quinoxalinone, acylamido derivs. 1204-06-4D, derivs. 1247-64-9, Pregnenolone sulfate 1247-64-9D, Pregnenolone sulfate, derivs. 1403-66-3, Gentamicin 1477-50-5D, Indole-2-carboxylic acid, derivs. 1744-22-5, Riluzole 1982-67-8, Methionine sulfoximine 2051-28-7D, Perhydroquinoline, derivs. 2067-84-7D, derivs. 2379-57-9, DNQX 2835-06-5D, 2-Amino-2-phenylacetic acid, derivs. 2922-83-0D, Kynurenine, derivs. 3106-85-2 3153-26-2 3466-80-6D, derivs. 3947-46-4D, derivs. 4210-66-6 4294-45-5, D,L-threo-3-Hydroxyaspartic acid **4368-28-9**, **Tetrodotoxin** 5094-12-2D, derivs. 6329-61-9D, Decahydroisoquinoline, derivs. 6624-49-3, 3-Isoquinolinecarboxylic acid 6729-55-1, .gamma.-D-Glutamylglycine 6740-88-1, Ketamine 6740-88-1D, Ketamine, derivs. 7083-63-8D, 4-Aminofluorene, derivs. 7439-95-4D, Magnesium, salts, biological studies 7440-66-6D, Zinc, salts, biological studies 7620-28-2, D-.alpha.-Aminoadipic acid 9046-27-9, .gamma.-Glutamyl transpeptidase 10024-97-2, Nitrous oxide, biological studies 11120-54-0D, Oxadiazole, derivs. 12766-00-6D, Quinazolinone, derivs. 12794-10-4D, Benzodiazepine, derivs. 13392-28-4, Rimantadine 13517-64-1, (.+-.)-.beta.-Cyclazocine 13598-36-2D, Phosphonic acid, derivs. 14176-49-9, Tiletamine 14176-49-9D, Tiletamine, derivs. 14277-97-5D, Domoic acid, derivs. 14333-18-7, Orthovanadate 15151-57-2D, derivs. 15804-19-0D, Quinoxaline-2,3(1H,4H)dione, derivs. 16450-41-2, L-Glutamic acid diethyl ester 16561-29-8, 12-O-Tetradecanoylphorbol-13-acetate 16804-55-0 18000-24-3, 7-Chlorokynurenic acid 19253-87-3, L-Methioninehydroxamic acid 19982-08-2, Memantine 19982-08-2D, Memantine, derivs. 21124-40-3D, derivs. 21500-98-1, TCP 21500-98-1D, TCP, derivs. 21820-30-4, (-)-.beta.-Cyclazocine 21820-35-9, (+)-.beta.-Cyclazocine 22059-21-8, 1-Aminocyclopropanecarboxylic acid 22071-15-4, Ketoprofen 22264-50-2, 1-Amino-1-cyclobutanecarboxylic acid 23210-56-2, Ifenprodil 23210-56-2D, Ifenprodil, derivs. 23715-85-7D, Isoquinolinium, derivs., salts 24167-43-9 25451-15-4, Felbamate 26469-60-3D, Quinoline carboxylic acid, derivs. 27774-13-6 29966-04-9D, derivs. 31321-68-3D, derivs. 35015-91-9D, derivs. 35251-84-4D, derivs. 36412-06-3 42413-70-7D, 3,6-Pyridazinedione, derivs. 50537-17-2D, derivs. 50624-35-6D, derivs. 52274-74-5D, Piperidine carboxylic acid, derivs. 52851-41-9D, 2,4(1H,3H)-Quinolinedione, derivs. 53123-88-9, Rapamycin 53123-88-9D, Rapamycin, derivs. 53774-74-6 54951-68-7D, Aminophenylacetic acid, derivs. 56223-47-3D, derivs. 56995-20-1, Flupirtine 56995-20-1D, Flupirtine, derivs. 57734-57-3D, 2-Aminomethylpyrrolidine, 1-aryl derivs. 57982-78-2, Budipine 57982-78-2D, Budipine, derivs. 60142-96-3, Gabapentin 62653-26-3D, derivs. 63291-47-4D, 2,3-Quinoxalinedione, derivs. 64294-96-8D, 9H-Fluorenamine, derivs. 65842-67-3D, derivs. 69768-79-2, .alpha.-Monofluoromethylputrescine 72956-09-3, Carvedilol 72956-09-3D, Carvedilol, derivs. 74214-63-4D, .beta.-Carboline-3-carboxylic acid, derivs. 76075-27-9D, Imidazo[1,2-a]pyrimidine-2-carboxamide, derivs. 76326-31-3 77086-22-7, Dizocilpine maleate 77086-22-7D, MK801, derivs. 77521-29-0D, .alpha.-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, derivs. 78944-89-5 79055-68-8, D-2-Amino-5-phosphonovaleric acid 80985-55-3D, derivs. 82717-30-4D, esters and amides 83689-34-3D, derivs. 84057-84-1, Lamotrigine 88192-22-7 90237-02-8, GAMS 93438-65-4, Conantokin G 93438-65-4D, Conantokin G, derivs. 97240-79-4, Topiramate 100828-16-8, CPP 102771-26-6, GYKI 52466 104534-80-7D, Quinolinone, derivs. 107886-50-0 110347-85-8, Selfotel 112924-45-5, HU 211 112924-45-5D, Dexanabinol, derivs. 115066-14-3, CNQX 116049-53-7, CGP 40116 117414-74-1, D-CPP-ene 117571-54-7, NPC 12626 118876-58-7, NBQX 119431-25-3, Eliprodil 120667-19-8, PD 129635 123929-99-7 123931-04-4 124070-15-1, ADCI 125412-11-5 125546-04-5, LY 233053 126114-66-7, FR115427 127476-26-0, Conantokin T 127910-31-0, CGP 37849 127910-32-1, CGP 39551 128298-28-2, Remacemide 128298-28-2D, Remacemide, derivs. 129920-05-4 129938-34-7, MDL 100453

130775-79-0, MS-153   130800-90-7, BW619C89   131475-40-6D, derivs.
132472-31-2, CGP 39653   132715-28-7D, derivs.   134234-12-1, CP101606
135840-49-2   136109-04-1, LY274614   136845-59-5, LY 233536
137160-11-3, CNS1102   137160-11-3D, CNS1102, derivs.   137424-81-8
137433-06-8, LY235959   138047-56-0, CP 283097
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for cancer treatment)

IT 140187-23-1   140187-23-1D, derivs.   140202-46-6, SC 48981   140202-48-8
142235-88-9, PD 130527   143692-48-2, GYKI 53655   144301-37-1, NPC 17742
144425-86-5, BW1003C87   144665-07-6, Lubeluzole   147600-11-1
150045-04-8D, Histogranin (cattle), derivs.   153322-06-6, FPL 15896AR
153436-38-5, GV150526   153504-81-5, ACEA1021   154106-40-8D, derivs.
154106-92-0, RPR 104632   154164-30-4, YM90K   154652-83-2, LY293558
156484-30-9D, derivs.   156694-78-9   157068-35-4   162434-68-6D, derivs.
164150-09-8, S 17625-2   171866-31-2   172901-45-0D, derivs.
172901-60-9D, derivs.   175408-34-1   178165-43-0   189894-57-3
192565-05-2D, derivs.   195988-65-9, Ro 8-4304   206260-33-5
210245-80-0, YM872   216382-88-6D, Imidazopyridine, derivs.   254751-28-5, NS 1209   270902-29-9D, 4H-2,3-Benzodiazepin-4-one, derivs.
270902-30-2D, derivs.   270902-31-3D, derivs.   270902-32-4D, derivs. and stereoisomers   270902-33-5   270902-34-6D, derivs.   270902-35-7D, derivs.   270902-36-8D, derivs.   270902-37-9D, 4-Quinolinesulfonamide, derivs.   270902-38-0D, derivs.   270902-39-1D, derivs.   270902-41-5D, derivs.   270902-42-6D, derivs.   270902-43-7   270902-43-7D, derivs.
270902-44-8D, 2-Benzocyclodecenamine, derivs.   270902-45-9D, esters
270902-46-0D, derivs.   270902-47-1D, Imidazo[1,2-a]pyrazin-5(1H)-one, derivs.   270902-48-2D, derivs.   270902-49-3   270902-50-6
270921-46-5D, derivs.   270921-47-6D, derivs.   270921-49-8D, derivs.
270921-50-1D, derivs.   270921-51-2D, derivs.   270921-52-3D, derivs.
270921-54-5D, Pyridinedione, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for cancer treatment)

IT 50-07-7, Mitomycin C   50-18-0, Cyclophosphamide   50-44-2, 6-Mercaptopurine   50-76-0, Actinomycin D   51-21-8, 5-Fluorouracil
52-24-4, Thiotepa   53-03-2, Prednisone   55-86-7, Nitrogen mustard
55-98-1, Busulfan   57-22-7, Vincristine   59-05-2, Methotrexate
83-43-2, Methylprednisolone   120-73-0D, Purine, analogs   147-94-4, Cytosine arabinoside   148-82-3, Melphalan   154-42-7, 6-Thioguanine
154-93-8, BCNU   289-95-2D, Pyrimidine, analogs   305-03-3, Chlorambucil
446-86-6, Azathioprine   671-16-9, Procarbazine   865-21-4, Vinblastine
4342-03-4, Dacarbazine   9014-02-2, Neocarzinostatin   11056-06-7, Bleomycin   13010-20-3D, Nitrosourea, derivs.   13010-47-4, CCNU
13909-09-6, Methyl-CCNU   15663-27-1, Cisplatin   20830-81-3, Daunorubicin
23214-92-8, Doxorubicin   33419-42-0, Etoposide   41575-94-4, Carboplatin
65271-80-9, Mitoxantrone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for cancer treatment, and combinations with other agents)

IT 56-86-0, L-Glutamic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutamate release inhibitors and synthesis inhibitors; glutamate antagonists for cancer treatment)

RE.CNT 8   THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) American Home Prod; EP 0778023 A 1997 CAPLUS
(2) Ben-Eliyahu, S; PROCEEDINGS OF THE WESTERN PHARMACOLOGY SOCIETY 1993, V36, P293 CAPLUS
(3) Chaudieu, I; J NEUROCHEM 1993, V61(suppl), PS255

(4) Igarashi, K; JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1995, V272(3), P1101 CAPLUS
(5) Olney, J; EP 0432994 A 1991 CAPLUS
(6) Seiler, N; INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY 1998, V30(3), P393 CAPLUS
(7) Surendra, S; US 4885171 A 1989 CAPLUS
(8) Yamada, K; COLLOQ INT CENT NAT RECH SCI 1971, 197, P311

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DEFAULT):end

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L52  ANSWER 1 OF 18  CAPLUS  COPYRIGHT 2003 ACS on STN
AN   2002:905867  CAPLUS
DN   137:363099
TI   Analgesic composition and method
IN   Ku, Baoshan; Shum, Frank Hay Kong
PA   Wex Medical Instrumentation Co., Ltd., Peop. Rep. China
SO   PCT Int. Appl., 35 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  A61K031-517
     ICS  A61K031-485; A61P025-04
CC   1-11 (Pharmacology)
     Section cross-reference(s): 63
FAN.CNT 1
     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
     ---------------  ----  --------       ---------------  --------
PI   WO 2002094272     A1   20021128       WO 2002-CN339    20020520
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CN 1386505        A    20021225       CN 2001-118098   20010518
     US 2002198226     A1   20021226       US 2002-62483    20020205
PRAI CN 2001-118098    A    20010518
AB   A pharmaceutical analgesic compn. comprising an opioid analgesic
     agent and a compd. that binds to the SS1 or SS2 subunit of a sodium
     channel, such as tetrodotoxin and saxitoxin, and analogs
     thereof.  Administration of an opioid analgesic agent and a
     compd. that binds to the SS1 or SS2 subunit of a sodium channel, such as
     tetrodotoxin and saxitoxin, and their analogs, produces analgesia
     in the treatment of pain in mammals.  For example, the synergistic
     analgesia effect produced by co-administering tetrodotoxin (TTX)
     and morphine was obsd. in a formalin test in rats.  Morphine used alone at
     0.30 mg/kg only produced 10.2% inhibition of formalin-induced pain.
     Combination of TTX at 0.19 .mu.g/kg with morphine at 2.50 mg/kg increased
     the inhibition rate to 86.7% from 34.9% where the latter was used alone.
     TTX at a dose of 0.39 .mu.g/kg (1/50 of LD50) produced an inhibition rate
     of 32.9% when used alone and 66.2% in combination with 0.15 mg/kg of
     morphine, whereas the latter only produced an inhibition rate of 7.2% when
     used alone.
ST   opioid sodium channel blocker injection synergistic
     analgesic
IT   Sodium channel
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (SS1 or SS2 subunit; synergistic analgesic activity of
        combination of opioid and sodium channel blocker)
IT   Drug delivery systems
        (injections, i.m.; synergistic analgesic activity of
        combination of opioid and sodium channel blocker)
IT   Drug delivery systems
        (injections, intrathecal; synergistic analgesic activity of
        combination of opioid and sodium channel blocker)
IT   Ion channel blockers
```

(sodium; **synergistic** analgesic activity of combination of **opioid** and sodium channel blocker)

IT Analgesics
(**synergistic** analgesic activity of combination of **opioid** and sodium channel blocker)

IT **Opioids**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**synergistic** analgesic activity of combination of **opioid** and sodium channel blocker)

IT Drug interactions
(**synergistic; synergistic** analgesic activity of combination of **opioid** and sodium channel blocker)

IT 52-26-6, Morphine hydrochloride 57-27-2, Morphine, biological studies 76-57-3, Codeine 76-99-3, Methadone 437-38-7, Fentanyl **3270-35-7**, Tetrodonic acid **4368-28-9**, **Tetrodotoxin 7724-38-1**, Tetrodaminotoxin **7724-39-2**, **Methoxytetrodotoxin 7724-40-5**, **Ethoxytetrodotoxin 7724-41-6**, **Deoxytetrodotoxin 13072-89-4**, **Anhydrotetrodotoxin 35523-89-8**, Saxitoxin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**synergistic** analgesic activity of combination of **opioid** and sodium channel blocker)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Anon; US 4022899 1977 CAPLUS
(2) Anon; CN 1145225 A 1997 CAPLUS
(3) Xur, Y; JIANGSU CLINICAL MEDICAL JOURNAL 2001, V5(5), P361

L52 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:317692 CAPLUS
DN 137:320198
TI Peripheral antinociceptive action of morphine and the **synergistic** interaction with lamotrigine
AU Arguelles, Carlos F.; Torres-Lopez, Jorge E.; Granados-Soto, Vinicio
CS Laboratorio de Farmacologia, Centro Nacional de Rehabilitacion, Mex.
SO Anesthesiology (2002), 96(4), 921-925
CODEN: ANESAV; ISSN: 0003-3022
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-11 (Pharmacology)

AB Background: Lamotrigine inhibits glutamate release through the preferential blockade of voltage-dependent Na+ channels. In contrast, morphine reduces release of excitatory amino acids through the activation of **opioid** receptors and also inhibits **tetrodotoxin** -resistant Na+ channels on peripheral afferent neurons. The current study was designed to investigate the antinociceptive effects of locally administered morphine and lamotrigine. The interaction between morphine and lamotrigine at the periphery was also examd. Methods: Morphine, lamotrigine, or a combination of morphine and lamotrigine was administered locally to female Wistar rats, and the antinociceptive effect was detd. in the formalin test. Isobolog. analyses were used to define the nature of the functional interactions between morphine and lamotrigine. Results: Peripheral administration of either morphine or lamotrigine produced a dose-related antinociceptive effect. Isobolog. analyses revealed that peripheral morphine and lamotrigine interacted **synergistically** in the formalin test. Conclusions: The study shows a functional interaction between lamotrigine and morphine at the peripheral level.

ST antinociceptive peripheral morphine lamotrigine analgesic **synergistic** interaction

IT Analgesia

Analgesics
(peripheral antinociceptive action of morphine and the **synergistic** interaction with lamotrigine)

IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(peripheral antinociceptive action of morphine and the **synergistic** interaction with lamotrigine)

IT Nervous system
(peripheral; peripheral antinociceptive action of morphine and the **synergistic** interaction with lamotrigine)

IT Drug interactions
(**synergistic**; peripheral antinociceptive action of morphine and the **synergistic** interaction with lamotrigine)

IT 56-86-0, L-Glutamic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(peripheral antinociceptive action of morphine and the **synergistic** interaction with lamotrigine)

IT 57-27-2, Morphine, biological studies 84057-84-1, Lamotrigine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peripheral antinociceptive action of morphine and the **synergistic** interaction with lamotrigine)

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Advokat, C; Brain Res 1995, V699, P157 CAPLUS
(2) Aguirre-Banuelos, P; Eur J Pharmacol 2000, V395, P9 CAPLUS
(3) Belozertseva, I; Eur J Pharmacol 2000, V396, P77 CAPLUS
(4) Bonicalzi, V; Surgery 1997, V122, P567 MEDLINE
(5) Canavero, S; Pain 1996, V68, P179 CAPLUS
(6) Carlton, S; Brain Res 1998, V790, P160 CAPLUS
(7) Carlton, S; Neurosci Lett 1995, V197, P25 CAPLUS
(8) Chapman, V; Brain Res 1992, V28, P321
(9) Cheung, H; Epilepsy Res 1992, V13, P107 CAPLUS
(10) Coderre, T; J Neurosci 1992, V12, P3665 CAPLUS
(11) Coggeshall, R; Brain Res 1997, V764, P126 CAPLUS
(12) Davidson, E; Brain Res 1998, V785, P136 CAPLUS
(13) Davidson, E; Neuroreport 1997, V8, P941 CAPLUS
(14) Devulder, J; J Pain Symptom Management 2000, V19, P398 MEDLINE
(15) Dickenson, A; Neurosci Lett 1987, V83, P207 MEDLINE
(16) Ferreira, S; Eur J Pharmacol 1991, V217, P121
(17) Ferreira, S; Prostaglandins 1979, V18, P191 CAPLUS
(18) Gold, M; Proc Natl Acad Sci U S A 1996, V93, P1108 CAPLUS
(19) Granados-Soto, V; Eur J Pharmacol 1997, V287, P281
(20) Grass, S; Acta Physiol Scand 1996, V158, P269 CAPLUS
(21) Hong, Y; Eur J Pharmacol 1995, V277, P21 CAPLUS
(22) Hunter, J; Eur J Pharmacol 1997, V324, P153 CAPLUS
(23) Klamt, J; Anesthesiology 1998, V88, P487 CAPLUS
(24) Leach, M; Epilepsia 1986, V27, P490 CAPLUS
(25) Lees, G; Brain Res 1993, V612, P190 CAPLUS
(26) Levine, J; Neuroscience 1989, V32, P571 CAPLUS
(27) Lutfy, K; Pharmacol Res 1999, V40, P435 CAPLUS
(28) McCleane, G; Pain 1999, V83, P105 CAPLUS
(29) McCleane, G; Pain Clin 1998, V11, P69
(30) Mixcoatl-Zecuatl, T; Eur J Pharmacol 2000, V400, P81 CAPLUS
(31) Nakamura-Craig, M; Pain 1995, V63, P33 CAPLUS
(32) Nishiyama, T; Anesthesiology 1998, V89, P715 CAPLUS
(33) Nishiyama, T; Eur J Pharmacol 2000, V395, P203 CAPLUS
(34) Ocana, M; Eur J Pharmacol 1990, V186, P377 CAPLUS
(35) Omote, K; Brain Res 1998, V787, P161 CAPLUS
(36) Parpura, V; J Neurosci 1995, V15, P5831 CAPLUS
(37) Piani, D; Neurosci Lett 1991, V133, P159 CAPLUS
(38) Russell, N; Neurosci Lett 1987, V76, P107 CAPLUS
(39) Stein, C; Anesth Analg 1993, V76, P182 MEDLINE
(40) Stein, C; J Pharmacol Exp Ther 1989, V248, P1269 CAPLUS

(41) Tallarida, R; Life Sci 1989, V45, P947 CAPLUS
(42) Tallarida, R; Psychopharmacol 1997, V133, P378 CAPLUS
(43) Webb, J; Pain 1998, V76, P357 CAPLUS
(44) Wong, C; Eur J Pharmacol 1996, V297, P27 CAPLUS
(45) Yaksh, T; Brain Res 1988, V458, P319 CAPLUS
(46) Yoshimura, M; Nature 1983, V305, P529 CAPLUS
(47) Zakrzewska, J; Pain 1997, V73, P223 CAPLUS
(48) Zimmermann, M; Pain 1983, V16, P109 MEDLINE

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L53  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   84057-84-1  REGISTRY
CN   1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
CN   BW 430C
CN   Lamictal
CN   Lamotrigin
CN   Lamotrigine
CN   LTG
FS   3D CONCORD
MF   C9 H7 Cl2 N5
CI   COM
SR   Commission of European Communities
LC   STN Files:   ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST,
       CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES,
       EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*,
       SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, WHO
         (**Enter CHEMLIST File for up-to-date regulatory information)
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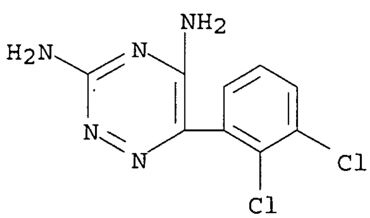


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               6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             667 REFERENCES IN FILE CAPLUS (1947 TO DATE)

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NOTICE SET TO OFF  FOR DISPLAY COMMAND
SET COMMAND COMPLETED
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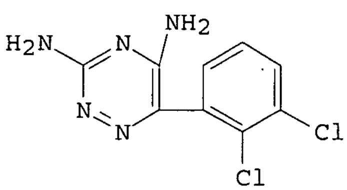
L58 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1993:116561 CAPLUS
DN 118:116561
TI An in vitro investigation of the action of lamotrigine on neuronal voltage-activated sodium channels
AU Cheung, Helen; Kamp, Dietgard; Harris, Eric
CS Dep. Biol., Fisons Pharm., Rochester, NY, 14623, USA
SO Epilepsy Research (1992), 13(2), 107-12
CODEN: EPIRE8; ISSN: 0920-1211
DT Journal
LA English
CC 1-11 (Pharmacology)
GI



I

AB Lamotrigine (LTG) (I) is a novel antiepileptic drug structurally unrelated to the major anticonvulsants in current use. Previous studies of LTG in rodents revealed efficacy in maximal electroshock test, pentylenetetrazol test and kindling models of seizures suggesting potential utility in the treatment of partial and generalized (tonic-clonic) seizures. In the present study, LTG was found to block sustained repetitive firing of sodium-dependent action potentials in mouse spinal cord cultured neurons and inhibit [3H]batrachotoxinin A 20-.alpha.-benzoate binding in rat brain synaptosomes suggesting a direct interaction with voltage-activated sodium channels.
ST lamotrigine antiepileptic sodium channel neuron
IT Anticonvulsants and Antiepileptics
(lamotrigine, neuronal voltage-activated sodium channels response to)
IT Nerve, composition
(voltage-activated sodium channels of, lamotrigine effect on, anticonvulsant activity in relation to)
IT Ion channel
(sodium, neuronal, voltage-activated, lamotrigine effect on, anticonvulsant activity in relation to)
IT **84057-84-1**, Lamotrigine
RL: **BIOL (Biological study)**
(neuronal voltage-activated **sodium channel** response to, anticonvulsant activity in relation to)

=>

L58 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:204925 CAPLUS
DN 139:63217
TI Binding of the Anticonvulsant Drug Lamotrigine and the Neurotoxin Batrachotoxin to Voltage-gated Sodium Channels Induces Conformational Changes Associated with Block and Steady-state Activation
AU Cronin, Nora B.; O'Reilly, Andrias; Duclohier, Herve; Wallace, B. A.
CS Birkbeck College, Department of Crystallography, University of London, London, WC1E 7HX, UK
SO Journal of Biological Chemistry (2003), 278(12), 10675-10682
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 1-11 (Pharmacology)
AB Voltage-gated sodium channels are dynamic membrane proteins characterized by rapid conformational changes that switch the mol. between closed resting, activated, and inactivated states. Sodium channels are specifically blocked by the anticonvulsant drug lamotrigine, which preferentially binds to the channel pore in the inactivated open state. Batrachotoxin is a lipid-sol. alkaloid that causes steady-state activation and binds in the inner pore of the sodium channel with overlapping but distinct mol. determinants from those of lamotrigine. Using CD spectroscopy on purified voltage-gated sodium channels from Electrophorus electricus, the secondary structures assocd. with the mixt. of states present at equil. in the absence of these ligands were compared with specific stabilized states in their presence. As the channel shifts to open states, there appears to be a significant change in secondary structure to a more .alpha.-helical conformation. The obsd. changes are consistent with increased order involving the S6 segments that form the pore, the domain III-IV linker, and the P-loops that form the outer pore and selectivity filter. A mol. model has been constructed for the sodium channel based on its homol. with the pore-forming regions of bacterial potassium channels, and automated docking of the crystal structure of lamotrigine with this model produces a structure in which the close contacts of the drug are with the residues previously identified by mutational studies as forming the binding site for this drug.
ST anticonvulsant lamotrigine neurotoxin batrachotoxin voltage gated sodium channel conformation
IT Anticonvulsants
Conformation
Molecular association
(binding of anticonvulsant drug lamotrigine and the neurotoxin batrachotoxin to voltage-gated sodium channels induces conformational changes assocd. with block and steady-state activation)
IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(voltage-gated; binding of anticonvulsant drug lamotrigine and the neurotoxin batrachotoxin to voltage-gated sodium channels induces conformational changes assocd. with block and steady-state activation)
IT **84057-84-1**, Lamotrigine
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); **BIOL (Biological study); USES (Uses)**
(binding of anticonvulsant drug lamotrigine and the neurotoxin batrachotoxin to voltage-gated **sodium channels**
induces conformational changes assocd. with block and steady-state activation)
RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Allen, P; J Clin Microbiol 1982, V15, P324 MEDLINE
(2) Altschul, S; Nucleic Acids Res 1997, V25, P3389 CAPLUS
(3) Andrade, M; Protein Eng 1993, V6, P383 CAPLUS
(4) Anger, T; J Med Chem 2001, V44, P115 CAPLUS

(5) Balser, J; J Mol Cell Cardiol 2001, V33, P599 CAPLUS
(6) Barton, G; Protein Eng 1993, V6, P37 CAPLUS
(7) Bendahhou, S; C R Acad Sci (Paris) 1991, V312, P277 CAPLUS
(8) Bezanilla, F; Physiol Rev 2000, V80, P555 CAPLUS
(9) Brahms, S; J Mol Biol 1980, V138, P149 CAPLUS
(10) Brunger, A; Acta Crystallogr Sect D Biol Crystallogr 1998, V54, P904
(11) Chapman, M; Biophys J 1997, V72, P708 CAPLUS
(12) Chen, Y; Biophys Chem 1997, V65, P65 CAPLUS
(13) Chen, Z; J Biol Chem 2002, V277, P24653 CAPLUS
(14) Collaborative Computational Project; Acta Crystallogr Sect D Biol Crystallogr 1994, V50, P760
(15) Cormier, J; J Biol Chem 2002, V277, P9233 CAPLUS
(16) del Camino, D; Nature 2000, V403, P321 CAPLUS
(17) Doyle, D; Science 1998, V280, P69 CAPLUS
(18) Goldin, A; Neuron 2000, V28, P365 CAPLUS
(19) Goodsell, D; J Mol Recognit 1996, V9, P1 CAPLUS
(20) Hanke, W; Biochem Bioenerg J 1984, V12, P329 CAPLUS
(21) Hanlon, M; Biochemistry 2002, V41, P2886 CAPLUS
(22) Heinemann, S; Braz J Med Biol Res 1994, V27, P2781 CAPLUS
(23) Hille, B; Ionic Channels of Excitable Membranes. 3rd Ed 2001
(24) James, W; Biochemistry 1989, V28, P6001 CAPLUS
(25) Janes, R; Acta Crystallogr Sect C Cryst Struct Commu 1989, V45, P129
(26) Jiang, Y; Nature 2002, V417, P523 CAPLUS
(27) Keynes, R; Novartis Found Symp 2001, V241, P5
(28) Koorsgaard, M; Pflugers Arch Eur J Physiol 2001, V443, P18
(29) Kuroda, Y; Biophys J 1999, V77, P1363 CAPLUS
(30) Laemmli, U; Nature 1970, V227, P680 CAPLUS
(31) Lehmann-Horn, F; Physiol Rev 1999, V79, P1317 CAPLUS
(32) Levinson, R; Ion Channels 1990, V2, P33
(33) Li, R; J Biol Chem 2001, V276, P11072 CAPLUS
(34) Lobley, A; Bioinformatics 2002, V18, P211 CAPLUS
(35) Mao, D; Biochemistry 1984, V23, P2667 CAPLUS
(36) McPhee, J; J Biol Chem 1998, V273, P1121 CAPLUS
(37) Merril, C; Science 1981, V211, P1437 CAPLUS
(38) Miller, J; Biochemistry 1983, V22, P462 CAPLUS
(39) Narahashi, T; Adv Neurol 1999, V79, P457 MEDLINE
(40) Narahashi, T; Ann N Y Acad Sci 1986, V479, P133 CAPLUS
(41) Nicholls, A; Proteins 1991, V11, P281 CAPLUS
(42) Noda, M; Nature 1984, V312, P121 CAPLUS
(43) Otoom, S; Cytobios 2001, V106(Suppl 1), P75
(44) Patten, C; FEBS Lett 1999, V463, P375 CAPLUS
(45) Patton, D; Proc Natl Acad Sci (U S A) 1992, V89, P10905 CAPLUS
(46) Perozo, E; Science 1999, V285, P73 CAPLUS
(47) Provencher, S; Biochemistry 1981, V20, P33 CAPLUS
(48) Ptacek, L; Disorders of Voluntary Muscle, 7th Ed 2001, P604
(49) Recio-Pinto, E; J Gen Physiol 1987, V90, P375 CAPLUS
(50) Sali, A; J Mol Biol 1993, V234, P779 CAPLUS
(51) Sato, C; Nature 2001, V409, P1047 CAPLUS
(52) Savitsky, A; Anal Chem 1964, V36, P1627
(53) Smith, P; Anal Biochem 1985, V150, P76 CAPLUS
(54) Sreerama, N; Anal Biochem 2000, V287, P243 CAPLUS
(55) Sreerama, N; Anal Biochem 2000, V282, P252
(56) Sreerama, N; Prot Science 1999, V8, P370 CAPLUS
(57) Stuhmer, W; Nature 1989, V339, P597 MEDLINE
(58) Thompson, J; Nucleic Acids Res 1994, V22, P4673 CAPLUS
(59) vanStokkum, I; Anal Biochem 1990, V191, P110 CAPLUS
(60) Vedantham, V; Biophys J 2000, V78, P2943 CAPLUS
(61) Wallace, B; Anal Biochem 1984, V142, P317 CAPLUS
(62) Wallace, B; Biochemistry 1987, V26, P65 CAPLUS
(63) Wang, S; Biophys J 1999, V76, P3141 CAPLUS
(64) Wang, S; Biophys J 2000, V79, P1379 CAPLUS
(65) Wang, S; Mol Pharmacol 2001, V59, P1100 CAPLUS
(66) Wang, S; Proc Natl Acad Sci (U S A) 1998, V95, P2653 CAPLUS
(67) Wartenberg, H; Basic Res Cardiol 2001, V96, P645 CAPLUS

(68) Xie, X; Pflugers Arch Eur J Physiol 1995, V430, P437 CAPLUS
(69) Yarov-Yarovoy, V; J Biol Chem 2001, V276, P20 CAPLUS
(70) Zhang, H; Biochim Biophys Acta 2000, V1467, P406 CAPLUS
(71) Zhou, Y; Nature 2001, V414, P43 CAPLUS

L58 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:141957 CAPLUS
DN 139:95293
TI Differential interactions of lamotrigine and related drugs with transmembrane segment IVS6 of voltage-gated sodium channels
AU Liu, G.; Yarov-Yarovoy, V.; Nobbs, M.; Clare, J. J.; Scheuer, T.; Catterall, W. A.
CS Department of Pharmacology, University of Washington, Seattle, WA, 98195-7280, USA
SO Neuropharmacology (2003), 44(3), 413-422
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-11 (Pharmacology)
AB Voltage-gated sodium channels are blocked by local anesthetic and anticonvulsant drugs. A receptor site for local anesthetics has been defined in transmembrane segment S6 in domain IV (IVS6) of the .alpha. subunit, but the anticonvulsant lamotrigine and related compds. have more complex structures than local anesthetics and may interact with addnl. amino acid residues. Apparent KD values for inactivated-state block of rat brain type IIA sodium channels expressed in Xenopus oocytes were 31.9 .mu.M, 17.3 .mu.M, 3.7 .mu.M and 10.3 .mu.M for lamotrigine and compds. 227c89, 4030w92 and 619c89, resp. Compd. 619c89 was the strongest frequency-dependent blocker, which correlated with higher affinity and a five-fold slower recovery from drug block compared to lamotrigine. Examn. of lamotrigine block of mutant sodium channel .alpha. subunits, in which alanine had been substituted for each individual amino acid in IVS6, identified mutations I1760A, F1764A and Y1771A as causing the largest redns. in affinity (six-, seven- and 12-fold, resp.). The ratios of effects of these three mutations differed for compds. 227c89, 4030w92, and 619c89. The amino acid residues interacting with these pore-blocking drugs define a surface of IVS6 that is exposed to the pore and may rotate during gating.
ST lamotrigine anticonvulsant transmembrane segment sodium channel brain
IT Anticonvulsants
Brain
(differential interactions of lamotrigine and related drugs with transmembrane segment IVS6 of voltage-gated sodium channels)
IT Sodium channel
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(voltage-gated; differential interactions of lamotrigine and related drugs with transmembrane segment IVS6 of voltage-gated sodium channels)
IT **84057-84-1**, Lamotrigine 130800-90-7, 619c89 189013-61-4, 4030w92 333968-29-9, 227c89
RL: PAC (Pharmacological activity); **BIOL (Biological study)**
(differential interactions of lamotrigine and related drugs with transmembrane segment IVS6 of voltage-gated **sodium channels**)
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bean, B; Journal of General Physiology 1983, V81, P613 CAPLUS
(2) Butterworth, J; Anesthesiology 1990, V72, P711 CAPLUS
(3) Catterall, W; Physiological Reviews 1992, V72, PS15 CAPLUS
(4) Catterall, W; Trends in Pharmacological Sciences 1987, V8, P57 CAPLUS
(5) Courtney, K; European Journal of Pharmacology 1983, V88, P1 CAPLUS
(6) Courtney, K; Journal of Pharmacology and Experimental Therapeutics 1980, V213, P114 CAPLUS

(7) Doyle, D; Science 1998, V280, P69 CAPLUS
(8) Durell, S; Journal of Structural Biology 1998, V121, P263 CAPLUS
(9) Ehring, G; Journal of Pharmacology and Experimental Therapeutics 1988, V244, P479 CAPLUS
(10) Goldin, A; Proceedings of the National Academy of Sciences of the United States of America 1986, V83, P7503 CAPLUS
(11) Hennig, L; Biotechniques 1999, V26, P1170 CAPLUS
(12) Hille, B; Journal of General Physiology 1977, V69, P497 CAPLUS
(13) Holmgren, M; Neuron 1998, V21, P617 CAPLUS
(14) Hondeghem, L; Biochimica et Biophysica Acta 1977, V472, P373 CAPLUS
(15) Isom, L; Cell 1995, V83, P433 CAPLUS
(16) Isom, L; Science 1992, V256, P839 CAPLUS
(17) Kuo, C; British Journal of Pharmacology 1997, V121, P1231 CAPLUS
(18) Kuo, C; Molecular Pharmacology 1994, V46, P716 CAPLUS
(19) Leach, M; Stroke 1993, V24, P1063 CAPLUS
(20) Li, H; Molecular Pharmacology 1999, V55, P134 CAPLUS
(21) Matsuki, N; Journal of Pharmacology and Experimental Therapeutics 1984, V228, P523 CAPLUS
(22) McPhee, J; Journal of Biological Chemistry 1995, V270, P12025 CAPLUS
(23) Perozo, E; Science 1999, V285, P73 CAPLUS
(24) Ragsdale, D; Proceedings of the National Academy of Sciences of the United States of America 1996, V93, P9270 CAPLUS
(25) Ragsdale, D; Science 1994, V265, P1724 CAPLUS
(26) Striessnig, J; Proceedings of the National Academy of Sciences of the United States of America 1990, V87, P9108 CAPLUS
(27) Trezise, D; British Journal of Pharmacology 1998, V124, P953 CAPLUS
(28) Weiser, T; Molecular Pharmacology 1999, V56, P1238 CAPLUS
(29) Willow, M; Molecular Pharmacology 1984, V25, P228 CAPLUS
(30) Willow, M; Molecular Pharmacology 1985, V27, P549 CAPLUS
(31) Wright, S; Molecular Pharmacology 1998, V54, P733 CAPLUS
(32) Xie, X; Neuroscience 1996, V73, P951 CAPLUS
(33) Xie, X; Pflugers Archiv European Journal of Physiology 1995, V430, P437 CAPLUS
(34) Yarov-Yarovoy, V; Journal of Biological Chemistry 2001, V276, P20 CAPLUS
(35) Yarov-Yarovoy, V; Journal of Biological Chemistry 2002, V277, P35393 CAPLUS

L58 ANSWER 3 OF 17 CAPLUS

AN 2002:778717 CAPLUS
DN 137:273229
TI Norepinephrine and dopamine reuptake inhibitors for treating neuropathic pain
IN Quessy, Steven Noel; Rudd, George David; Winnem, Michael Fredrik
PA USA
SO U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-537
ICS A61K031-55; A61K031-53
NCL 514231200
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002147196	A1	20021010	US 2002-115548	20020403
PRAI	US 2001-281635P	P	20010405		

AB This invention relates to a compn. and method for alleviating neuropathic pain and/or its symptoms. The compn. for alleviation of neuropathic pain and/or its symptoms comprises (1) a compd. that inhibits the reuptake of both norepinephrine and dopamine or inhibits the reuptake of norepinephrine alone, in combination with (2) a compd. that acts as a sodium channel blocker. For example, the combination of lamotrigine and

bupropion demonstrates a synergy using the two compds. in the neuropathy model in rats. This may be evident by a greater efficacy against paw withdrawal threshold or von Frey monofilaments in individual rats, efficacy in a greater no. of rats, equiv. efficacy with the combination using lower doses of each agent, faster onset of action with the combination, or longer lasting pain relief.

ST dopamine norepinephrine reuptake inhibitor sodium channel blocker neuropathy

IT Nerve, disease
(neuropathy; norepinephrine and dopamine reuptake inhibitors in combination with sodium channel blocker for treating neuropathic pain)

IT Ion channel blockers
(sodium; norepinephrine and dopamine reuptake inhibitors in combination with sodium channel blocker for treating neuropathic pain)

IT Drug delivery systems
(suspensions; norepinephrine and dopamine reuptake inhibitors in combination with sodium channel blocker for treating neuropathic pain)

IT Drug delivery systems
(sustained-release; norepinephrine and dopamine reuptake inhibitors in combination with sodium channel blocker for treating neuropathic pain)

IT Drug interactions
(synergistic; norepinephrine and dopamine reuptake inhibitors in combination with sodium channel blocker for treating neuropathic pain)

IT Drug delivery systems
(tablets; norepinephrine and dopamine reuptake inhibitors in combination with sodium channel blocker for treating neuropathic pain)

IT 51-41-2, Norepinephrine 51-61-6, Dopamine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(norepinephrine and dopamine reuptake inhibitors in combination with sodium channel blocker for treating neuropathic pain)

IT 34911-55-2, Bupropion **84057-84-1**, Lamotrigine
RL: PAC (Pharmacological activity); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(norepinephrine and dopamine reuptake inhibitors in combination with **sodium channel** blocker for treating neuropathic pain)

L58 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:630008 CAPLUS
DN 138:280983
TI Antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity
AU Farber, N. B.; Jiang, X-P.; Heinkel, C.; Nemmers, B.
CS Department of Psychiatry, Washington University, St Louis, MO, USA
SO Molecular Psychiatry (2002), 7(7), 726-733
CODEN: MOPSFQ; ISSN: 1359-4184
PB Nature Publishing Group
DT Journal
LA English
CC 1-11 (Pharmacology)
AB N-methyl-D-aspartate (NMDA) glutamate receptor antagonists are used in clin. anesthesia and are being developed as therapeutic agents for preventing neurodegeneration in stroke, epilepsy, and brain trauma. However, the ability of these agents to produce neurotoxicity in adult rats and psychosis in adult humans compromises their clin. usefulness. In addn., an NMDA receptor hypofunction (NRHypo) state might play a role in neurodegenerative and psychotic disorders, like Alzheimer's disease, bipolar disorder and schizophrenia. Thus, developing pharmacol. means of preventing these NRHypo-induced effects could have significant clin. relevant benefits. NRHypo neurotoxicity appears to be mediated by a complex disinhibition mechanism that results in the excessive stimulation of certain vulnerable neurons. Here we report our findings that five agents (phenytoin, carbamazepine, valproic acid, lamotrigine, and riluzole), thought to possess anticonvulsant activity because they inhibit voltage-gated sodium channels, prevent NRHypo neurotoxicity. The ability

of tetrodotoxin, a highly selective inhibitor of voltage-gated sodium channels, to prevent the same neurotoxicity suggests that inhibition of this ion channel is the likely mechanism of action of these five agents. We also found that three other anticonvulsants (felbamate, gabapentin and ethosuximide), whose mechanism is less clear, also prevent NRHypo neurotoxicity, suggesting that inhibition of voltage-gated sodium channels is not the only mechanism via which anticonvulsants can act to prevent NRHypo neurotoxicity. Several of these agents have been found to be of clin. use in bipolar disorder. It would be of interest to det. whether these agents might have therapeutic benefits for conditions in which a NRHypo state may exist.

ST antiepileptic neuroprotectant voltage gated sodium channel NMDA antagonist neurotoxicity

IT Glutamate antagonists
(NMDA antagonists; antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA-binding; antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT Anticonvulsants
(antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT Cytoprotective agents
(neuroprotectants; antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT Toxicity
(neurotoxicity; antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT Nerve
(toxicity; antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(voltage-gated; antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT 77086-22-7, MK801
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(NMDA antagonist; antiepileptic drugs and agents that inhibit voltage-gated sodium channels prevent NMDA antagonist neurotoxicity)

IT 57-41-0, Phenytoin 77-67-8, Ethosuximide 99-66-1, Valproic acid 298-46-4, Carbamazepine 1744-22-5, Riluzole 25451-15-4, Felbamate 60142-96-3, Gabapentin **84057-84-1**, Lamotrigine
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(antiepileptic drugs and agents that inhibit voltage-gated **sodium channels** prevent NMDA antagonist neurotoxicity)

RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Allen, H; Science 1990, V247, P221 CAPLUS
(2) Altshuler, L; Bipolar Dis 1999, V1, P61 MEDLINE
(3) Anand, A; Arch Gen Psychiatry 2000, V57, P270 CAPLUS
(4) Binnie, C; Epilepsy:A Comprehensive Textbook 1997, P1531
(5) Bowden, C; Arch Gen Psychiatry 2000, V57, P481 CAPLUS
(6) Bowden, C; JAMA 1994, V271, P1830
(7) Bowden, C; JAMA 1994, V271, P918 MEDLINE
(8) Calabrese, J; Am J Psychiatry 2000, V157, P1523 MEDLINE
(9) Calabrese, J; J Clin Psychiatry 1999, V60, P79 CAPLUS
(10) Calabrese, J; J Clin Psychiatry 2000, V61, P841 CAPLUS
(11) Chadwick, D; Epilepsy:A Comprehensive Textbook 1997, P1521
(12) Corso, T; Brain Res 1997, V752, P1 CAPLUS
(13) Domino, E; PCP (Phencyclidine): Historical and Current Perspectives 1981, P401

(14) Ellison, G; Neuroreport 1993, V5, P17 CAPLUS
(15) Farber, N; Arch Gen Psychiatry 1999, V56, P13 MEDLINE
(16) Farber, N; Child and Early Adolescent Bipolar Disorder, in press 2002
(17) Farber, N; Mol Psychiatry 2002, V7, P32 CAPLUS
(18) Ghaemi, S; J Affect Disord 2001, V65, P167 CAPLUS
(19) Greil, W; Int Clin Psychopharmacol 1999, V14, P277 MEDLINE
(20) Greil, W; Int Clin Psychopharmacol 1999, V14, P283 MEDLINE
(21) Horvath, Z; Brain Res 1997, V753, P181 CAPLUS
(22) Ishimaru, M; Neurosci Lett 1995, V193, P1 CAPLUS
(23) Javitt, D; Am J Psychiatry 1991, V148, P1301 MEDLINE
(24) Jevtovic-Todorovic, V; J Cereb Blood Flow Metab 1997, V17, P168 CAPLUS
(25) Jiang, X; Soc Neurosci Abs 2001, V27, P973.4
(26) Lerer, B; J Clin Psychiatry 1987, V48, P89 MEDLINE
(27) Lowe, D; Neurochem Int 1994, V25, P583 CAPLUS
(28) Macdonald, R; Curr Opin Neurol 1997, V10, P121 MEDLINE
(29) Macdonald, R; Epilepsy:A Comprehensive Textbook 1997, P1383
(30) McCabe, R; J Pharmacol Exp Therapeut 1993, V264, P1248 CAPLUS
(31) Mishory, A; Am J Psychiatry 2000, V157, P463 MEDLINE
(32) Mizoule, J; Neuropharmacology 1995, V24, P767
(33) Moore, J; J Gen Physiol 1967, V50, P1401 CAPLUS
(34) Olney, J; Arch Gen Psychiatry 1995, V52, P998 CAPLUS
(35) Olney, J; Arch Neurol 1997, V54, P1234 MEDLINE
(36) Olney, J; Science 1989, V244, P1360 CAPLUS
(37) Olney, J; Science 1991, V254, P1515 CAPLUS
(38) Pande, A; Bipolar Dis 2000, V2, P249 MEDLINE
(39) Paxinos, G; The Rat Brain in Stereotaxic Coordinates, 4th edn 1998
(40) Pisani, A; Br J Pharmacol 1995, V116, P2053 CAPLUS
(41) Pope, H; Arch Gen Psychiatry 1991, V48, P62
(42) Prakriya, M; Neuron 2000, V26, P671 CAPLUS
(43) Rho, J; Ann Neurol 1994, V35, P229 CAPLUS
(44) Schoepp, D; J Pharmacol Exp Therapeut 1990, V255, P1301 CAPLUS
(45) Shank, R; Epilepsia 2000, V41(Suppl 1), PS3
(46) Small, J; Arch Gen Psychiatry 1991, V48, P915 MEDLINE
(47) Swinyard, E; Epilepsia 1986, V27, P27 CAPLUS
(48) Taglialatela, M; Eur J Pharmacol 1996, V316, P373 CAPLUS
(49) Takata, M; J Gen Physiol 1966, V49, P977 CAPLUS
(50) Taylor, C; Trends Pharmacol Sci 1995, V16, P309 CAPLUS
(51) Tekin, S; J Neural Transm Suppl 1998, V105, P295 CAPLUS
(52) Ulas, J; Neuroscience 1997, V79, P973 CAPLUS
(53) Urbanska, E; Eur J Pharmacol 1991, V200, P277 CAPLUS
(54) Vogt, B; Neurobiology of Cingulate Cortex and Limbic Thalamus 1993, P19
(55) Wenk, G; Neurobiol Aging 1991, V12, P93 CAPLUS
(56) Zarnowski, T; Neuropharmacology 1994, V33, P619 CAPLUS
(57) Zona, C; Neuroscience 1998, V85, P931 CAPLUS

L58 ANSWER 5 OF 17 CAPLUS

AN 2002:456293 CAPLUS
DN 138:100764

TI A comparison of the anti-nociceptive effects of voltage-activated Na+ channel blockers in the formalin test

AU Blackburn-Munro, Gordon; Ibsen, Nete; Erichsen, Helle K.
CS Department of Pharmacology, NeuroSearch A/S, Ballerup, DK-2750, Den.

SO European Journal of Pharmacology (2002), 445(3), 231-238
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-11 (Pharmacology)

AB We have used the rat formalin test to compare the anti-nociceptive properties of several voltage-activated Na+ channel blockers. The antiarrhythmic mexiletine (37.5 and 50 mg/kg, i.p.) attenuated flinching behavior in both first and second phases of the test compared with vehicle ($P<0.05$). The anti-convulsants lamotrigine (15 and 30 mg/kg, i.p.) and carbamazepine (20 mg/kg, i.p.) also inhibited second phase flinching

behavior compared with vehicle ($P<0.05$), although phenytoin (up to 40 mg/kg, i.p.) was without effect. Riluzole (5 mg/kg, i.p.), in contrast to lubeluzole (up to 10 mg/kg, i.p.) also inhibited second phase flinching behavior compared with vehicle ($P<0.05$). When tested against an acute thermal nociceptive stimulus mexiletine, lubeluzole and riluzole exhibited anti-nociceptive effects. The anti-nociceptive doses used in the formalin test produced no motor impairment in the rotarod test. Thus, voltage-activated Na+ channel blockers can attenuate nociceptive behavior in the formalin test, and a specific mechanism of action on Na+ channel function may be required for this to occur.

ST analgesic sodium channel blocker mexiletine lamotrigine carbamazepine riluzole lubeluzole; phenytoin sodium channel blocker analgesic mexiletine lamotrigine carbamazepine

IT Analgesics
(analgesic effects of voltage-activated sodium channel blockers in formalin test)

IT Nervous system, disease
(ataxia; analgesic effects of voltage-activated sodium channel blockers in formalin test)

IT Behavior
(flinching; analgesic effects of voltage-activated sodium channel blockers in formalin test)

IT Behavior
(motor, disorder; analgesic effects of voltage-activated sodium channel blockers in formalin test)

IT Ion channel blockers
(sodium; analgesic effects of voltage-activated sodium channel blockers in formalin test)

IT 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 298-46-4, Carbamazepine 1744-22-5, Riluzole 31828-71-4, Mexiletine **84057-84-1**, Lamotrigine 144665-07-6, Lubeluzole
RL: PAC (Pharmacological activity); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(analgesic effects of voltage-activated **sodium channel** blockers in formalin test)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Abbott, F; Pain 1995, V60, P91 MEDLINE
(2) Arner, S; Pain 1988, V33, P11 MEDLINE
(3) Ashton, D; Brain Res 1997, V745, P210 CAPLUS
(4) Backonja, M; Neuropathic Pain:Pathophysiology and Treatment Progress in Pain Research and Management 2001, P185 CAPLUS
(5) Baker, M; Trends Pharmacol Sci 2001, V22, P27 CAPLUS
(6) Blackburn-Munro, G; NeuroReport 1997, V8, P1549 CAPLUS
(7) Brau, M; Anesthesiology 2001, V94, P137 CAPLUS
(8) Canavero, S; Pain 1996, V68, P179 CAPLUS
(9) Catterall, W; Trends Pharmacol Sci 1987, V8, P57 CAPLUS
(10) Chaplan, S; J Pharmacol Exp Ther 1997, V280, P829 CAPLUS
(11) Chapman, V; Pain 1998, V77, P289 CAPLUS
(12) Coderre, T; J Neurosci 1992, V12, P3665 CAPLUS
(13) Culmsee, C; Eur J Pharmacol 1998, V342, P193 CAPLUS
(14) Dickenson, A; Pain 1987, V30, P349 CAPLUS
(15) Eglen, R; Trends Pharmacol Sci 1999, V20, P337 CAPLUS
(16) Erichsen, H; Pain, in press 2002
(17) Gold, M; Proc Natl Acad Sci U S A 1996, V93, P1108 CAPLUS
(18) Hargreaves, K; Pain 1988, V32, P77 MEDLINE
(19) Hunskaar, S; Pain 1987, V30, P103 CAPLUS
(20) Hunter, J; Eur J Pharmacol 1997, V324, P153 CAPLUS
(21) Jett, M; Pain 1997, V69, P161 CAPLUS
(22) Juilius, D; Nature 2001, V13, P203
(23) Kuo, C; Mol Pharmacol 2002, V51, P1077
(24) Laird, J; Br J Pharmacol 2001, V134, P1742 CAPLUS
(25) Lees, G; Brain Res 1993, V612, P190 CAPLUS
(26) Malmberg, A; Br J Pharmacol 1995, V114, P1069 CAPLUS

(27) Moore, R; BMJ 1998, V316, P333 CAPLUS
(28) Nakamura-Craig, M; Pain 1995, V63, P33 CAPLUS
(29) Ragsdale, D; Brain Res Rev 1998, V26, P16 CAPLUS
(30) Rush, A; Neurosci Lett 1997, V226, P95 CAPLUS
(31) Simmons, R; Neuropharmacology 1998, V37, P25 CAPLUS
(32) Tanelian, D; Pain Forum 1995, V4, P75
(33) Tate, S; Nat Neurosci 1998, V1, P653 CAPLUS
(34) Waxman, S; Pain 1999, VS6, PS133
(35) Woolf, C; Science 2000, V288, P1765 CAPLUS
(36) Xie, X; Soc Neurosci Abstr 1996, V22, P333
(37) Yashpal, K; Pain 2001, V94, P17 CAPLUS
(38) Zimmerman, M; Pain 1983, V16, P109

L58 ANSWER 6 OF 17 CAPLUS
AN 2002:275793 CAPLUS
DN 136:289081
TI Use of frequency dependent voltage activated sodium channel blockers in prevention of noise induced hearing loss
IN Etheridge, Steven
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-53
CC 1-11 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002028394	A1	20020411	WO 2001-EP11498	20011005

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 2002015923	A5	20020415	AU 2002-15923	20011005
	EP 1322312	A1	20030702	EP 2001-986260	20011005

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI GB 2000-24517 A 20001006
WO 2001-EP11498 W 20011005

AB The present invention provides the use of frequency dependent voltage activated sodium channel blockers particularly lamotrigine in the prevention of noise induced hearing loss. Lamotigine showed otoprotective effect in guinea pigs.

ST sodium channel blocker noise induced hearing loss; lamotrigine prevention noise induced hearing loss
IT Ear
(cochlea, perilymph; frequency dependent voltage activated sodium channel blockers in prevention of noise induced hearing loss)
IT Nerve
(cochlear; frequency dependent voltage activated sodium channel blockers in prevention of noise induced hearing loss)
IT Drug delivery systems
Electric potential
Frequency
(frequency dependent voltage activated sodium channel blockers in prevention of noise induced hearing loss)
IT Acoustic noise
(hearing loss induced by; frequency dependent voltage activated sodium

channel blockers in prevention of noise induced hearing loss)
IT Hearing
(loss, noise-induced; frequency dependent voltage activated sodium channel blockers in prevention of noise induced hearing loss)
IT Ion channel blockers
(sodium; frequency dependent voltage activated sodium channel blockers in prevention of noise induced hearing loss)
IT **84057-84-1**, Lamotrigine
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(frequency dependent voltage activated **sodium channel** blockers in prevention of noise induced hearing loss)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Simpson, J; THE AMERICAN JOURNAL OF OTOLOGY 1999, V20, P627 MEDLINE

AN 2002:31496 CAPLUS
DN 136:65968
TI A lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes
IN Korsgaard, Mads P. G.
PA Neurosearch A/s, Den.
SO PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K014-435
CC 6-1 (General Biochemistry)
Section cross-reference(s): 3
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002002608	A2	20020110	WO 2001-DK414	20010614
	WO 2002002608	A3	20020510		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	EP 1301596	A2	20030416	EP 2001-940247	20010614

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI	DK 2000-1049	A	20000705
	WO 2001-DK414	W	20010614

AB The present invention relates to a novel voltage gated sodium channel located in the brain, a cDNA encoding it, vectors and host cells contg. the same, transgenic non-human animal capable of expressing the sodium channel, and methods of screening for modulators of the channel such as modulators for use in the treatment of seizures, and conditions related to the limbic system and limbic regions including limbic seizures. The sodium channel, a sequence homolog of the rat RNAv1.5 channel was identified by RT-PCR during an anal. of sodium channel gene expression in HiB5 cells. The protein was more sensitive to inhibition by lamotrigine than the RNAv1.5 channel, suggesting that it may be a target for the treatment of epilepsy..
ST sodium channel RNAV15a rat lamotrigine sensitive cDNA cloning sequence
IT Drug screening
(for sodium channel effectors; lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)
IT Immunoglobulins

RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(fragments, to sodium channel RNAv1.5a; lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT Astrocyte
Epilepsy
Molecular cloning
(lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT Gene, animal
Sodium channel
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT Brain
(limbic system, sodium channels of; lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT Ion channel blockers
Ion channel openers
(sodium, screening for; lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT Antibodies
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(to sodium channel RNAv1.5a; lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT Mouse
(transgenic, sodium channel RNAv1.5 gene expression in; lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT 384961-58-4
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nucleotide sequence; lamotrigine-sensitive sodium channel RNAv1.5a from rat astrocytes)

IT **84057-84-1**, Lamotrigine
RL: BUU (Biological use, unclassified); **BIOL (Biological study)**; **USES (Uses)**
(**sodium channel** inhibited by; lamotrigine-sensitive **sodium channel** RNAv1.5a from rat astrocytes)

L58 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2001:759770 CAPLUS

DN 137:15274

TI Pharmacophore model for antiepileptic drugs acting on sodium channels

AU Tasso, Silvina M.; Bruno-Blanch, Luis E.; Estiu, Guillermina L.

CS Quim. Med., Dep. de Ciencias Biol., Fac. de Ciencias Exactas, Univ. Nacional de La Plata, La Plata, 1900, Argent.

SO Journal of Molecular Modeling [online computer file] (2001), 7(7), 231-239
CODEN: JMMOFK; ISSN: 0948-5023
URL: http://link.springer.de/link/service/journals/00894/papers/1007007/10070231.pdf

PB Springer-Verlag

DT Journal; (online computer file)

LA English

CC 1-3 (Pharmacology)

AB Fifteen antiepileptic drugs (AED), active against the maximal electroshock seizure test and able to block the neuronal voltage-dependent sodium channel, have been studied by a similarity anal. Structural and electronic, quantum chem. derived characteristics are compared. Rigid analogs are included, because of the flexibility of some structures, to discern the conformational requirements assocd. with these ligands in the moment of the interaction. An inactive compd. (ethosuximide) helps in the definition of the structural factors that are important for the activity. We propose a pharmacophore model that, giving an interpretation of the biol. activity, allows the design of new AED with a well-defined mechanism

of interaction.
ST antiepileptic sodium channel blocker pharmacophore similarity analysis
IT Similarity theory
(anal.; pharmacophore model for antiepileptic drugs acting on sodium channels)
IT Anticonvulsants
Conformation
Pharmacophores
(pharmacophore model for antiepileptic drugs acting on sodium channels)
IT Ion channel blockers
(sodium; pharmacophore model for antiepileptic drugs acting on sodium channels)
IT 57-41-0, Phenytoin 77-67-8, Ethosuximide 99-66-1, Valproic acid 298-46-4, Carbamazepine 25451-15-4, Felbamate 28721-07-5, Oxcarbazepine 42971-09-5, Vinpocetine 60142-96-3, Gabapentin 68291-97-4, Zonisamide **84057-84-1**, Lamotrigine 91077-32-6, Dezinamide 93738-40-0, Ralitoline 97240-79-4, Topiramate 106308-44-5, Rufinamide 128298-28-2, Remacemide
RL: PAC (Pharmacological activity); PRP (Properties); **BIOL (Biological study)**
(pharmacophore model for antiepileptic drugs acting on **sodium channels**)
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anon; Spartan, Wavefunction 1997
(2) Balbes, L; Reviews in computational chemistry 1994, P337 CAPLUS
(3) Bazil, C; Annu Rev Med 1998, V49, P135 CAPLUS
(4) Bialer, M; Epilepsy Res 1996, V25, P299 CAPLUS
(5) Brown, M; J Med Chem 1999, V42, P1537 CAPLUS
(6) Chen, A; Epilepsia 1963, V4, P66
(7) Dam, M; Antiepileptic drugs, 4th edn 1995, P987
(8) Delorenzo, R; Antiepileptic drugs, 4th edn 1995, P271
(9) Fariello, R; Antiepileptic drugs, 4th edn 1995, P581
(10) Ferrendelli, J; Antiepileptic drugs, 3rd edn 1989, P653
(11) Frisch, M; Gaussian 98 1998
(12) Gladding, G; Handbook of experimental pharmacology 1985, P341
(13) Gram, L; Antiepileptic drugs, 3rd edn 1989, P947
(14) Leach, J; CNS Drugs 1997, V8(5), P366 CAPLUS
(15) Leach, M; Antiepileptic drugs, 4th edn 1995, P861
(16) Loscher, W; Epilepsy Res 1994, V17, P95 CAPLUS
(17) Macdonald, R; Antiepileptic drugs, 4th edn 1995, P491
(18) Maryanoff, B; J Med Chem 1998, V41, P1315 CAPLUS
(19) Meldrum, B; Epilepsia 1996, V37(6), P4
(20) Molnar, P; Eur J Pharmacol 1995, V273, P303 CAPLUS
(21) Porter, R; Clev Clin Q 1984, V51, P293 MEDLINE
(22) Ragsdale, D; Brain Res Rev 1998, V26, P16 CAPLUS
(23) Rogawski, M; J Pharm Rev 1990, V42(3), P223 CAPLUS
(24) Shank, R; Epilepsia 1994, V35, P450 CAPLUS
(25) Stewart, J; Mopac, version 7.0 Research Laboratory 1994
(26) Tasso, S; Int J Quant Chem 1997, V65, P1107 CAPLUS
(27) Tasso, S; J Mol Struct (Theochem) 2000, V504, P229 CAPLUS
(28) Taylor, C; Antiepileptic drugs, 4th edn 1995, P829
(29) Taylor, C; Jasper's basic mechanisms of the epilepsies, 3rd edn:advances in neurology 1999, P1011 MEDLINE
(30) Unverferth, K; J Med Chem 1998, V41, P63 CAPLUS
(31) Wilder, B; Neurology 1995, V45(2), P7
(32) Willow, M; Mol Pharmacol 1982, V22, P627 CAPLUS
(33) Willow, M; Mol Pharmacol 1984, V25, P228 CAPLUS

L58 ANSWER 9 OF 17 CAPLUS
AN 2001:716121 CAPLUS
DN 136:243757
TI Inhibition of voltage-dependent sodium channels suppresses the functional magnetic resonance imaging response to forepaw somatosensory activation in

the rodent

AU Kida, Ikuhiro; Hyder, Fahmeed; Behar, Kevin L.
CS Department of Diagnostic Radiology, Yale University, New Haven, CT, 06510, USA

SO Journal of Cerebral Blood Flow and Metabolism (2001), 21(5), 585-591
CODEN: JCBMDN; ISSN: 0271-678X
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 8-6 (Radiation Biochemistry)
Section cross-reference(s): 13

AB Results of recent studies suggest that the glutamate-glutamine neurotransmitter cycle between neurons and astrocytes plays a major role in the generation of the functional imaging signal. In the current study, the authors tested the hypothesis that activation of voltage-dependent Na+ channels is involved in the blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) responses during somatosensory activation. The BOLD fMRI and cerebral blood flow (CBF) expts. were performed at 7 T on .alpha.-chloralose-anesthetized rats undergoing forepaw stimulation before and for successive times after application of lamotrigine, a neuronal voltage-dependent Na+ channel blocker and glutamate release inhibitor. The BOLD fMRI signal changes in response to forepaw stimulation decreased in a time-dependent manner from 6.7% .+-. 0.7% before lamotrigine injection to 3.0% .+-. 2.5% between 60 and 105 min after lamotrigine treatment. After lamotrigine treatment, the fractional increase in CBF during forepaw stimulation was an order of magnitude less than that obsd. before the treatment. Lamotrigine had no effect on baseline CBF in the somatosensory cortex in the absence of stimulation. These results strongly suggest that activation of voltage-dependent Na+ channels is involved in the BOLD fMRI responses during somatosensory activation of the rat cortex.

ST sodium channel brain MRI somatosensory activation

IT Imaging
(NMR; inhibition of voltage-dependent sodium channels suppresses the functional MRI response to forepaw somatosensory activation in rodent)

IT Circulation
(cerebral; inhibition of voltage-dependent sodium channels suppresses the functional MRI response to forepaw somatosensory activation in rodent)

IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of voltage-dependent sodium channels suppresses the functional MRI response to forepaw somatosensory activation in rodent)

IT Brain
(somatosensory cortex; inhibition of voltage-dependent sodium channels suppresses the functional MRI response to forepaw somatosensory activation in rodent)

IT **84057-84-1**, Lamotrigine
RL: BSU (Biological study, unclassified); **BIOL (Biological study)**
(inhibition of voltage-dependent **sodium channels** suppresses the functional MRI response to forepaw somatosensory activation in rodent)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Brinker, G; Magn Reson Med 1999, V41, P469 MEDLINE
(2) Chapin, J; J Comp Neurol 1984, V229, P199 MEDLINE
(3) Cheung, H; Epilepsy Res 1992, V13, P107 CAPLUS
(4) Choi, D; J Neurosci 1987, V7, P357 CAPLUS
(5) Cholet, N; J Cereb Blood Flow Metab 1999, V19(Suppl 1), PS668
(6) Conroy, B; Anesthesiology 1999, V90, P844 CAPLUS
(7) Forman, S; J Cereb Blood Flow Metab 1998, V18, P1064 CAPLUS
(8) Hyder, F; J Appl Physiol 1998, V85, P554 MEDLINE
(9) Hyder, F; J Cereb Blood Flow Metab 1994, V14, P649 MEDLINE
(10) Hyder, F; J Cereb Blood Flow Metab 1997, V17, P1040 CAPLUS

(11) Hyder, F; J Cereb Blood Flow Metab 2000, V20, P485 MEDLINE
(12) Hyder, F; Proc Natl Acad Sci 1996, V93, P7612 CAPLUS
(13) Kida, I; J Cereb Blood Flow Metab 2000, V20, P847 MEDLINE
(14) Kuo, C; Br J Pharmacol 1997, V121, P1231 CAPLUS
(15) Leach, M; Epilepsia 1986, V27, P490 CAPLUS
(16) Lizasoain, I; J Neurochem 1995, V64, P636 CAPLUS
(17) Lu, X; Neurochem Res 1997, V22, P705 CAPLUS
(18) McCarthy, G; Cereb Cortex 1996, V6, P600 MEDLINE
(19) Ogawa, S; Biophys J 1993, V64, P803 CAPLUS
(20) Ogawa, S; Proc Natl Acad Sci 1992, V89, P5951 MEDLINE
(21) Ogawa, S; Proc Natl Acad Sci 2000, V97, P11026 CAPLUS
(22) Pellerin, L; Proc Natl Acad Sci 1994, V91, P10625 CAPLUS
(23) Rothman, D; Philos Trans R Soc Lond B Biol Sci 1999, V354, P1165 CAPLUS
(24) Sibson, N; Proc Natl Acad Sci 1998, V95, P316 CAPLUS
(25) Siesjoe, B; Brain energy metabolism 1978, P237
(26) Silva, A; J Cereb Blood Flow Metab 1999, V19, P871 MEDLINE
(27) Siniscalchi, A; Synapse 1998, V30, P371 CAPLUS
(28) Smith, S; Epilepsy Res 1993, V15, P101 CAPLUS
(29) Smith, S; Stroke 1995, V26, P117 CAPLUS
(30) Sokoloff, L; Dev Neurosci 1996, V18, P343 CAPLUS
(31) Southam, E; Eur J Pharmacol 1998, V358, P19 CAPLUS
(32) Taylor, C; Adv Pharmacol 1997, V39, P47 CAPLUS
(33) Ueki, M; J Cereb Blood Flow Metab 1988, V8, P486 MEDLINE
(34) von Wegerer, J; Eur Neuropsychopharmacol 1997, V7, P77 MEDLINE
(35) Vriend, J; Life Sci 1997, V61, P2467 CAPLUS

L58 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:895811 CAPLUS
DN 134:231785
TI Effect of a neuronal sodium channel blocker on magnetic resonance derived indices of brain water content during global cerebral ischemia
AU Koinig, H.; Williams, J. P.; Quast, M. J.; Zornow, M. H.
CS Department of Anesthesiology and General Intensive Care, University of Vienna, Vienna, Austria
SO Brain Research (2000), 887(2), 301-308
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-11 (Pharmacology)
Section cross-reference(s): 2, 14
AB Diffusion-weighted magnetic resonance imaging (DWI) with calcn. of the apparent diffusion coeff. (ADC) of water is a widely used noninvasive method to measure movement of water from the extracellular to the intracellular compartment during cerebral ischemia. Lamotrigine, a neuronal Na+ channel blocker, has been shown to attenuate the increase in extracellular concns. of excitatory amino acids (EAA) during ischemia and to improve neurol. and histol. outcome. Because of its proven ability to reduce EAA levels during ischemia, lamotrigine should also minimize excitotoxic-induced increases in intracellular water content and therefore attenuate changes in the ADC. In this study, we sought to det. the effect of lamotrigine on intra- and extracellular water shifts during transient global cerebral ischemia. Fifteen New Zealand white rabbits were anesthetized and randomized to one of three groups: a control group, a lamotrigine-treated group, or a sham group. After being positioned in the bore of the magnet, a 12-min 50-s period of global cerebral ischemia was induced by inflating a neck tourniquet. During ischemia and early reperfusion there was a similar and significant decrease of the ADC in both the lamotrigine and control group. The ADC in the sham ischemia group remained at baseline throughout the expt. Lamotrigine-mediated blockade of voltage-gated sodium channels did not prevent the intracellular movement of water during 12 min 50 s of global ischemia, as measured by the ADC, suggesting that the ADC decline may not be mediated by voltage-gated sodium influx and glutamate release.

ST   brain ischemia edema sodium channel lamotrigine
IT   Imaging
        (NMR; effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   Brain
     Disease models
        (effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   Amino acids, biological studies
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
        (excitatory; effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   Biological transport
        (influx; effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   Brain, disease
        (ischemia; effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   Ion channel blockers
        (sodium; effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   **84057-84-1**, Lamotrigine
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **BIOL (Biological study)**
        (effect of a neuronal **sodium channel** blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   7732-18-5, Water, biological studies
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
        (effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   56-86-0, L-Glutamic acid, biological studies
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
IT   7440-23-5, Sodium, biological studies
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
        (transport; effect of a neuronal sodium channel blocker on magnetic resonance derived indexes of brain water content during global cerebral ischemia)
RE.CNT 38   THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Bacher, A; Anesthesiology 1997, V86, P459 CAPLUS
(2) Baker, A; J Neurochem 1991, V57, P1370 CAPLUS
(3) Belayev, L; Stroke 1998, V29, P2587 CAPLUS
(4) Bizzi, A; AJNR Am J Neuroradiol 1993, V14, P1347 MEDLINE
(5) Bizzi, A; Magn Reson Imaging 1996, V14, P581 MEDLINE
(6) Chandra, S; Pharmacology 1999, V58, P292 CAPLUS
(7) Conroy, B; Anesthesiology 1999, V90, P844 CAPLUS
(8) Davis, D; Magn Reson Med 1994, V31, P454 MEDLINE
(9) Dijkhuizen, R; J Cereb Blood Flow Metab 1999, V19, P341 CAPLUS
(10) Fischer, M; Magn Reson Imaging 1995, V13, P781 MEDLINE
(11) Fitton, A; Drugs 1995, V50, P691 CAPLUS
(12) Fujimori, H; Magn Reson Med 1998, V39, P647 CAPLUS
(13) Germano, I; J Neurosurg 1989, V70, P612 MEDLINE
(14) Goldberg, M; J Neurosci 1993, V13, P3510 CAPLUS
(15) Harris, N; J Cereb Blood Flow Metab 2000, V20, P28 CAPLUS

(16) Helpern, J; Proceedings SNMR 11th Annual Meeting 1992, P1201
(17) Hossmann, K; Cerebrovasc Brain Metab Rev 1995, V7, P187 MEDLINE
(18) Hossmann, K; J Cereb Blood Flow Metab 1994, V14, P723 MEDLINE
(19) Kimelberg, H; J Neurosurg 1995, V83, P1051 MEDLINE
(20) Kwon, J; Exp Neurol 1999, V159, P105 CAPLUS
(21) Minematsu, K; Neurology 1992, V42, P235 MEDLINE
(22) Minematsu, K; Stroke 1992, V23, P1304 MEDLINE
(23) Moseley, M; Magn Reson Med 1990, V14, P330 MEDLINE
(24) Nagatomo, Y; NMR Biomed 1995, V8, P265 CAPLUS
(25) Newman, M; Circulation 1994, V90(2), P243
(26) Pierpaoli, C; J Cereb Blood Flow Metab 1996, V16, P892 MEDLINE
(27) Roach, G; New Engl J Med 1996, V335, P1857 MEDLINE
(28) Schulz, J; J Cereb Blood Flow Metab 1995, V15, P948 CAPLUS
(29) Siesjo, B; J Neurosurg 1992, V77, P337 CAPLUS
(30) Sotanicmi, K; Ann Thorac Surg 1995, V59, P1336
(31) Szatkowski, M; Trends Neurosci 1994, V17, P359 CAPLUS
(32) Tatlisumak, T; Stroke 1998, V29, P850 CAPLUS
(33) Taylor, D; Neurochem Res 1996, V21, P1013 CAPLUS
(34) Urban, I; A Stereotaxic Atlas of the New Zealand Rabbit's Brain 1972, P1
(35) Urenjak, J; Pharmacol Rev 1996, V48, P21 CAPLUS
(36) Wahl, G; Chest 1996, V110, P1394 MEDLINE
(37) Waldmeier, P; Neurology 1995, V45, P1907 MEDLINE
(38) Yenari, M; Brain Res 1996, V739, P36 CAPLUS

L58 ANSWER 11 OF 17 CAPLUS
AN 2000:741960 CAPLUS
DN 133:305611
TI Sodium channel blocker compositions for treating or preventing chronic pain or convulsion
IN Lan, Nancy C.
PA Cocensys, Inc., USA
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-06
ICS A61K031-55; A61K031-53; A61K031-195; A61P029-00
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000061188	A1	20001019	WO 2000-US9387	20000410

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	EP 1169060	A1	20020109	EP 2000-923183	20000410

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	JP 2002541215	T2	20021203	JP 2000-610520	20000410
	US 2002037926	A1	20020328	US 2001-971007	20011005
PRAI	US 1999-128543P	P	19990409		
	WO 2000-US9387	W	20000410		

AB Methods of treating or preventing chronic pain or convulsion are disclosed by administering to an animal a sodium channel blocker and at least one of gabapentin and pregabalin. Also disclosed are pharmaceutical compns. and kits for the treatment or prevention of chronic pain or convulsion. Combination of 1.25 mg/kg oral Co 102862 and 25 mg/kg s.c. gabapentin had

synergistic effect in Chung model of neuropathic rats and much greater withdrawal threshold was obsd. than either compd. alone.

ST sodium channel blocker pain convulsion gabapentin

IT Pain
(chronic; sodium channel blocker compns. for treating or preventing chronic pain or convulsion)

IT Nerve, disease
(diabetic neuropathy; sodium channel blocker compns. for treating or preventing chronic pain or convulsion)

IT Nerve, disease
(neuralgia, terminal; sodium channel blocker compns. for treating or preventing chronic pain or convulsion)

IT Analgesics
Convulsion
Drug delivery systems
(sodium channel blocker compns. for treating or preventing chronic pain or convulsion)

IT Ion channel blockers
(sodium; sodium channel blocker compns. for treating or preventing chronic pain or convulsion)

IT 298-46-4, Carbamazepine 60142-96-3, Gabapentin **84057-84-1**, Lamotrigine 148553-50-8, Pregabalin. 181144-66-1, Co 102862
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(**sodium channel** blocker compns. for treating or preventing chronic pain or convulsion)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Algos Pharmaceutical Corporation; WO 9807447 A 1998 CAPLUS
(2) Societe de Conseils de Recherches Et D'Applications Scientifiques; FR 2756738 A 1998 CAPLUS
(3) Solaro, C; EUROPEAN JOURNAL OF NEUROLOGY 1999, V6(4), P505 MEDLINE

AN 2000:487701 CAPLUS

DN 133:203290

TI Selective depression of low-release probability excitatory synapses by sodium channel blockers

AU Prakriya, Murali; Mennerick, Steven

CS Departments of Psychiatry and Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, 63110, USA

SO Neuron (2000), 26(3), 671-682
CODEN: NERNET; ISSN: 0896-6273

PB Cell Press

DT Journal

LA English

CC 2-8 (Mammalian Hormones)
Section cross-reference(s): 1, 13

AB Sodium channels (NaChs) play a central role in action potential generation and are uniquely poised to influence the efficacy of transmitter release. We evaluated the effect of partial NaCh blockade on two aspects of synaptic efficacy. First, we evaluated whether NaCh blockade accounts for the ability of certain drugs to selectively depress glutamate release. Second, we evaluated the contribution of NaChs to intraneuronal variability in glutamate release probability (pr). The antiglutamate drug riluzole nearly completely depresses glutamate excitatory postsynaptic currents (EPSCs) at concns. that barely affect GABAergic inhibitory postsynaptic currents (IPSCs). NaCh inhibition explains the selective depression. Unlike other presynaptic depressants, partial NaCh blockade increases paired-pulse EPSC depression. This result is explained by selective depression of low-pr synapses. We conclude that local variations in the action potential contribute to pr variability among excitatory synapses.

ST sodium channel AMPA NMDA glutamate receptor excitatory neurotransmission hippocampus; riluzole lamotrigine carbamazepine phenytoin sodium channel blocker anticonvulsant neurotransmission; GABA receptor postsynaptic inhibitory neurotransmission sodium transport axon

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(AMPA-binding; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Neurotransmission
(GABAergic, postsynaptic inhibitory; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT GABA receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GABAA; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NMDA-binding; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Electric potential
(biol., action; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Nerve
(cell body; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Biological transport
(channel-mediated; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Polarization
(depolarization, biol.; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Neurotransmission
(excitatory; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Neurotransmission
(glutamatergic; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Brain
(hippocampus; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Anticonvulsants
Axon
Synapse
(selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Ion channel blockers
(sodium; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT Sodium channel
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(voltage-gated; selective depression of low-release probability excitatory synapses by sodium channel blockers)

IT 57-41-0, Phenytoin 298-46-4, Carbamazepine 1744-22-5, Riluzole **84057-84-1**, Lamotrigine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **BIOL (Biological study)**
(selective depression of low-release probability excitatory synapses by **sodium channel** blockers)

IT 7440-23-5, Sodium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; selective depression of low-release probability excitatory synapses by sodium channel blockers)

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Atwood, H; Nature 1967, V215, P57 MEDLINE
(2) Bekkers, J; Proc Natl Acad Sci USA 1991, V88, P7834 MEDLINE
(3) Colbert, C; J Neurosci 1996, V16, P6676 CAPLUS
(4) Debono, M; Eur J Pharmacol 1993, V235, P283 CAPLUS
(5) Fink, M; EMBO J 1998, V17, P3297 CAPLUS
(6) Hashimoto, K; J Physiol (Lond) 1998, V506, P391 CAPLUS
(7) Hebert, T; Mol Pharmacol 1994, V45, P1055 CAPLUS
(8) Hessler, N; Nature 1993, V366, P569 CAPLUS
(9) Hille, B; Ionic Channels of Excitable Membranes 1992
(10) Hsu, S; Neuron 1996, V17, P501 CAPLUS
(11) Huang, C; J Pharmacol Exp Ther 1997, V282, P1280 CAPLUS
(12) Huettner, J; Proc Natl Acad Sci USA 1988, V85, P1307 CAPLUS
(13) Johannes, L; J Neurochem 1998, V71, P1127 CAPLUS
(14) Kilbride, J; Eur J Pharmacol 1998, V356, P149 CAPLUS
(15) Leach, M; Epilepsia 1986, V27, P490 CAPLUS
(16) Leach, M; Epilepsia 1991, V32, PS4 CAPLUS
(17) Louvel, E; Trends Pharmacol Sci 1997, V18, P196 CAPLUS
(18) MacIver, M; Anesthesiology 1996, V85, P626 MEDLINE
(19) Mackenzie, P; J Neurophysiol 1998, V80, P2089 MEDLINE
(20) Magee, J; Science 1995, V268, P301 CAPLUS
(21) Magleby, K; Synaptic Function 1987, P13
(22) Martin, D; Eur J Pharmacol 1993, V250, P473 CAPLUS
(23) Martina, M; J Physiol (Lond) 1997, V505, P593 CAPLUS
(24) Martina, M; Science 2000, V287, P295 CAPLUS
(25) Mennerick, S; J Neurophysiol 1995, V73, P320 MEDLINE
(26) Mennerick, S; J Physiol (Lond) 1995, V488, P85 CAPLUS
(27) Msghina, M; J Neurosci 1998, V18, P1374 CAPLUS
(28) Msghina, M; J Neurosci 1999, V19, P8419 CAPLUS
(29) Murthy, V; Neuron 1997, V18, P599 CAPLUS
(30) Obrenovitch, T; Trends Pharmacol Sci 1998, V19, P9 CAPLUS
(31) Rosenmund, C; Science 1993, V262, P754 CAPLUS
(32) Sather, W; J Physiol (Lond) 1992, V450, P643 CAPLUS
(33) Schikorski, T; J Neurosci 1997, V17, P5858 CAPLUS
(34) Song, J; J Pharmacol Exp Ther 1997, V282, P707 CAPLUS
(35) Stefani, A; Exp Neurol 1997, V147, P115 CAPLUS
(36) Stuart, G; Nature 1994, V367, P69 MEDLINE
(37) Stuart, G; Trends Neurosci 1997, V20, P125 CAPLUS
(38) Taylor, C; Trends Pharmacol Sci 1995, V16, P309 CAPLUS
(39) Umemiya, M; Br J Pharmacol 1995, V116, P3227 CAPLUS
(40) Zucker, R; Annu Rev Neurosci 1989, V12, P13 MEDLINE

L58 ANSWER 13 OF 17 CAPLUS

AN 1997:167436 CAPLUS

DN 126:207449

TI Lamotrigine inhibits extracellular glutamate accumulation during transient global cerebral ischemia in rabbits

AU Bacher, Andreas; Zornow, Mark H.

CS Department of Anesthesiology and General Intensive Care, University of Vienna, Austria

SO Anesthesiology (1997), 86(2), 459-463
CODEN: ANESAV; ISSN: 0003-3022

PB Lippincott-Raven

DT Journal

LA English
CC 1-11 (Pharmacology)
AB During cerebral ischemia, an influx of Na+ may be partially responsible for the release of the excitatory amino acid glutamate. When glutamate is released in excessive concns. during ischemia, it may become neurotoxic. The ability of the Na+ channel blocker lamotrigine to inhibit glutamate release during episodes of transient global cerebral ischemia was investigated. After approval was given by the animal care and use committee, 24 New Zealand white rabbits were randomly assigned to one of four groups each contg. six animals (control, L20, L50, and a hypothermic group). After anesthesia (1% halothane) was induced, the tracheas were intubated and the lungs mech. ventilated before microdialysis probes were placed in the hippocampus. Ninety minutes before the onset of ischemia, either 20 or 50 mg/kg lamotrigine was administered i.v. (in the L20 and L50 groups). Esophageal temp. was maintained at 38.degree. in the control, L20, and L50 groups, whereas the animals in the hypothermic group were cooled to 30.degree.. Two 10-min periods of cerebral ischemia, sepd. by a 90-min interval, were generated by inflating a neck tourniquet. High-performance liq. chromatog. was used to det. the glutamate concn. in the microdialyzate. Anal. of variance and Dunnett's test were used for statistical anal. Data are presented as means. During the first ischemic period, glutamate concn. increased only slightly from baseline. A significant increase was obsd. during the second ischemic period for the control (sixfold) and the L20 (threefold) groups. Glutamate concns. in the L50 and the hypothermic groups were significantly lower than in the other two groups and remained at the baseline level during the entire expt. This study shows that the Na+ channel blocker lamotrigine is effective in inhibiting extracellular glutamate accumulation during transient global cerebral ischemia. This attenuation of ischemia-induced glutamate release may explain the previously reported neuroprotective properties of Na+ channel blockers.
ST lamotrigine extracellular glutamate global cerebral ischemia
IT Brain, disease
(ischemia; sodium channel blocker lamotrigine inhibits extracellular glutamate accumulation during transient global cerebral ischemia in rabbits in relation to neuroprotective activity)
IT Cytoprotective agents
(neuroprotectants; sodium channel blocker lamotrigine inhibits extracellular glutamate accumulation during transient global cerebral ischemia in rabbits in relation to neuroprotective activity)
IT **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study); USES (Uses)**
(**sodium channel** blocker lamotrigine inhibits extracellular glutamate accumulation during transient global cerebral ischemia in rabbits in relation to neuroprotective activity)
IT 56-86-0, Glutamic acid, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sodium channel blocker lamotrigine inhibits extracellular glutamate accumulation during transient global cerebral ischemia in rabbits in relation to neuroprotective activity)

L58 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:638500 CAPLUS
DN 125:292832
TI Mechanism of action of lamotrigine
AU Garthwaite, J.
CS NEUROSCIENCE RESEARCH, GLAXO WELLCOME LTD, Beckenham, UK
SO International Congress and Symposium Series - Royal Society of Medicine (1996), 214(Lamotrigine--A Brighter Future), 63-68
CODEN: RMISDU; ISSN: 0142-2367
PB Royal Society of Medicine Press

DT Journal
LA English
CC 1-11 (Pharmacology)
AB Lamotrigine was originally found to inhibit the release of neurotransmitters, particularly glutamate, from brain tissue exposed to veratrine, a sodium channel opener, without influencing basal release or the release induced by other stimuli. This suggested that lamotrigine does not interfere with neurotransmitter release per se but probably exerts its actions by inhibiting brain sodium channels. Recent research has demonstrated that the drug, with an apparent affinity (12 .mu.M) appropriate to its therapeutically-effective concns., acts selectively on the slow inactivated state of the sodium channel. The effect is to stabilize the channel in this state, so preventing the generation of high-frequency epileptiform firing which would otherwise propagate, through excitatory circuits, into normal neighboring brain areas. A brief description of some of the exptl. evidence on the mechanism of action of lamotrigine is described in this article.
ST lamotrigine antiepileptic action mechanism; sodium channel lamotrigine antiepileptic mechanism
IT Anticonvulsants and Antiepileptics
(highly selective action of lamotrigine on slow inactivated state of sodium channel and antiepileptics action mechanism)
IT Ion channel
(sodium, highly selective action of lamotrigine on slow inactivated state of sodium channel and antiepileptics action mechanism)
IT **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(highly selective action of lamotrigine on slow inactivated state of **sodium channel** and antiepileptics action mechanism)

L58 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:816157 CAPLUS
DN 123:275729
TI Sodium-channel blockade and glutamate release: The mechanism of cerebroprotection by lamotrigine, BW 1003C87 and BW 619C89
AU Meldrum, B. S.; Smith, S. E.; Lekieffre, D.; Chapman, A. G.; Graham, J. L.; Pearce, P. C.
CS Department Neurology, Institute Psychiatry, London, SE5 8AF, UK
SO Pharmacology of Cerebral Ischemia 1994, [International Symposium on Pharmacology of Cerebral Ischemia] -- 5th, Marburg, July 20-22, 1994 (1994), 203-9. Editor(s): Krieglstein, Josef; Oberpichler-Schwenk, Heike. Publisher: Medpharm Scientific Publishers, Stuttgart, Germany.
CODEN: 61RMAY
DT Conference
LA English
CC 1-11 (Pharmacology)
AB The cerebroprotective effects in brain ischemia of the title compds. which block the increase of extracellular glutamate and aspartate are described. Their mechanism of action, which may include sodium channel blockade and affecting amino acid release, is discussed.
ST sodium channel blockade cerebroprotection lamotrigine analog; amino acid release cerebroprotection lamotrigine analog; brain ischemia cerebroprotection lamotrigine analog
IT Amino acids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sodium-channel blockade and amino acid release as mechanism of cerebroprotection by lamotrigine and BW 1003C87 and BW 619C89 in brain ischemia)
IT Brain, disease
(ischemia, sodium-channel blockade and amino acid release as mechanism of cerebroprotection by lamotrigine and BW 1003C87 and BW 619C89 in

brain ischemia)
IT Cytoprotective agents
(neuroprotectants, sodium-channel blockade and amino acid release as mechanism of cerebroprotection by lamotrigine and BW 1003C87 and BW 619C89 in brain ischemia)
IT Ion channel blockers
(sodium, sodium-channel blockade and amino acid release as mechanism of cerebroprotection by lamotrigine and BW 1003C87 and BW 619C89 in brain ischemia)
IT **84057-84-1**, Lamotrigine 130800-90-7, BW 619C89 144425-86-5, BW 1003C87
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(**sodium-channel** blockade and amino acid release as mechanism of cerebroprotection by lamotrigine and BW 1003C87 and BW 619C89 in brain ischemia)
IT 56-12-2, GABA, biological studies 56-41-7, Alanine, biological studies 56-84-8, Aspartic acid, biological studies 56-86-0, Glutamic acid, biological studies 107-35-7, Taurine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sodium-channel blockade and amino acid release as mechanism of cerebroprotection by lamotrigine and BW 1003C87 and BW 619C89 in brain ischemia)

L58 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1993:641243 CAPLUS
DN 119:241243
TI Lamotrigine, phenytoin and carbamazepine interactions on the sodium current present in N4TG1 mouse neuroblastoma cells
AU Lang, Daniel G.; Wang, Ching M.; Cooper, Barrtett R.
CS Div. Pharmacol., Burroughs Wellcome Co., Research Triangle Park, NC, USA
SO Journal of Pharmacology and Experimental Therapeutics (1993), 266(2), 829-35
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
CC 1-11 (Pharmacology)
AB Lamotrigine is a chem. novel anticonvulsant drug that has been reported to inhibit veratrine-induced neurotransmitter release from cortical slices in vitro. To characterize further the mechanism of action of lamotrigine, the authors have investigated the effects of this drug together with the anticonvulsant drugs phenytoin and carbamazepine on voltage-sensitive sodium channels present in N4TG1 mouse neuroblastoma clonal cells. Lamotrigine, phenytoin and carbamazepine produced a tonic inhibition of sodium channels with IC50 values of 91, 58 and 140 .mu.M, resp. At a concn. of 100 .mu.M, all compds. shifted the voltage-dependency of steady-state inactivation toward more neg. potentials by 7 to 15 mV, slowed the rate of recovery from inactivation and produced a use-dependent inhibition of sodium channels. The authors' data show that lamotrigine inhibits sodium channels in a manner that is similar to that produced by phenytoin and carbamazepine. This inhibition of neuronal activity is consistent with the redn. of glutamate release that was previously reported in neurochem. studies, and it expands the authors' understanding of the mechanism of action of this anticonvulsant drug.
ST lamotrigine anticonvulsant sodium channel; phenytoin anticonvulsant sodium channel; carbamazepine anticonvulsant sodium channel
IT Anticonvulsants and Antiepileptics
(lamotrigine, sodium channel blockade by)
IT Ion channel blockers
(sodium, lamotrigine, anticonvulsant activity in relation to)
IT 7440-23-5, Sodium, biological studies
RL: BIOL (Biological study)

(channel, lamotrigine blockade of, anticonvulsant activity in relation to)

IT 57-41-0, Phenytoin 298-46-4, Carbamazepine **84057-84-1**, Lamotrigine

RL: **BIOL (Biological study)**

(**sodium channel** blockade by, anticonvulsant activity in relation to)

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=> d l62 1-12 kwic, an,pi

L62  ANSWER 1 OF 12  CAPLUS  COPYRIGHT 2003 ACS on STN
TI   Antiepileptic drugs and agents that inhibit voltage-gated sodium
     channels prevent NMDA antagonist neurotoxicity
AB   . . . findings that five agents (phenytoin, carbamazepine, valproic
     acid, lamotrigine, and riluzole), thought to possess anticonvulsant
     activity because they inhibit voltage-gated sodium channels,
     prevent NRHypo neurotoxicity.  The ability of tetrodotoxin, a
     highly selective inhibitor of voltage-gated sodium channels, to
     prevent the same neurotoxicity suggests that inhibition of this ion
     channel is the likely mechanism of action of. . . other anticonvulsants
     (felbamate, gabapentin and ethosuximide), whose mechanism is less clear,
     also prevent NRHypo neurotoxicity, suggesting that inhibition of
     voltage-gated sodium channels is not the only mechanism via
     which anticonvulsants can act to prevent NRHypo neurotoxicity.  Several of
     these agents have. . .
ST   antiepileptic neuroprotectant voltage gated sodium channel NMDA
     antagonist neurotoxicity
IT   Glutamate antagonists
        (NMDA antagonists; antiepileptic drugs and agents that inhibit
        voltage-gated sodium channels prevent NMDA antagonist
        neurotoxicity)
IT   Glutamate receptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (NMDA-binding; antiepileptic drugs and agents that inhibit
        voltage-gated sodium channels prevent NMDA antagonist
        neurotoxicity)
IT   Anticonvulsants
        (antiepileptic drugs and agents that inhibit voltage-gated
        sodium channels prevent NMDA antagonist neurotoxicity)
IT   Cytoprotective agents
        (neuroprotectants; antiepileptic drugs and agents that inhibit
        voltage-gated sodium channels prevent NMDA antagonist
        neurotoxicity)
IT   Toxicity
        (neurotoxicity; antiepileptic drugs and agents that inhibit
        voltage-gated sodium channels prevent NMDA antagonist
        neurotoxicity)
IT   Nerve
        (toxicity; antiepileptic drugs and agents that inhibit voltage-gated
        sodium channels prevent NMDA antagonist neurotoxicity)
IT   Sodium channel
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (voltage-gated; antiepileptic drugs and agents that inhibit
        voltage-gated sodium channels prevent NMDA antagonist
        neurotoxicity)
IT   77086-22-7, MK801
     RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
        (NMDA antagonist; antiepileptic drugs and agents that inhibit
        voltage-gated sodium channels prevent NMDA antagonist
        neurotoxicity)
IT   57-41-0, Phenytoin   77-67-8, Ethosuximide   99-66-1, Valproic acid
     298-46-4, Carbamazepine   1744-22-5, Riluzole   25451-15-4, Felbamate
     60142-96-3, Gabapentin 84057-84-1, Lamotrigine
     RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (antiepileptic drugs and agents that inhibit voltage-gated
        sodium channels prevent NMDA antagonist neurotoxicity)
AN   2002:630008  CAPLUS
DN   138:280983
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L62 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . Na+ channels. In contrast, morphine reduces release of excitatory amino acids through the activation of opioid receptors and also inhibits **tetrodotoxin**-resistant Na+ channels on peripheral afferent neurons. The current study was designed to investigate the antinociceptive effects of locally administered morphine. . . .
IT **Sodium** channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(peripheral antinociceptive action of morphine and the synergistic interaction with lamotrigine)
IT 57-27-2, Morphine, biological studies **84057-84-1**, Lamotrigine
RL: PAC (Pharmacological activity); THU (Therapeutic use); **BIOL (Biological study); USES (Uses)**
(peripheral antinociceptive action of morphine and the synergistic interaction with lamotrigine)
AN 2002:317692 CAPLUS
DN 137:320198

L62 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . precursor cells expressed a voltage-gated Na+ channel with electrophysiol. characteristics shifted to more neg. voltages and a lower sensitivity to **tetrodotoxin** [concn. required for half-maximal inhibition (IC50) 0.9 .mu.M] compared with endogenous neuronal Na+ channels. The channel activation and steady-state inactivation. . . .
ST **sodium** channel Nav15a cDNA sequence RNA splicing brain; RNA splicing Nav15a lamotrigine sipatrigine brain stem cell
IT Biological transport
(**sodium**; identification of novel voltage-gated Na+ channel rNav1.5a in rat hippocampal progenitor stem cell line HiB5)
IT **Sodium** channel
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(voltage-gated, Nav1.5a isoform; identification of novel voltage-gated Na+ channel rNav1.5a in rat hippocampal progenitor stem cell line HiB5)
IT **84057-84-1**, Lamotrigine 130800-90-7, Sipatrigine
RL: PKT (Pharmacokinetics); **BIOL (Biological study)**
(identification of novel voltage-gated Na+ channel rNav1.5a in rat hippocampal progenitor stem cell line HiB5 and its blockade by lamotrigine and sipatrigine)
IT 7440-23-5, **Sodium**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; identification of novel voltage-gated Na+ channel rNav1.5a in rat hippocampal progenitor stem cell line HiB5)
AN 2001:802166 CAPLUS
DN 137:122592

L62 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . equil. potential. The half-maximal activation and inactivation voltages were -24 mV and -63 mV, resp. Currents were reversibly blocked by **tetrodotoxin** with a half-maximal inhibition of 13 nM. The effects of four commonly used anti-convulsant drugs were examd. for the first. . . . the cloned human type IIA channel. Lamotrigine and phenytoin produced concn.- and voltage-dependent inhibition of the type IIA currents, whereas, **sodium** valproate and gabapentin (.ltoreq.1 mM) had no effect. These results indicate that recombinant human type IIA Na+ channels conduct **tetrodotoxin**-sensitive Na+ currents with similar properties to those obsd. in recombinant rat brain type IIA and native rat brain Na+ channels.. . . .
ST **sodium** channel brain electrophysiol pharmacol anticonvulsant
IT Biological transport
Ion channel blockers
(**sodium**; electrophysiol. and pharmacol. properties of human brain type IIA Na+ channel expressed in a stable mammalian cell line in relation to effect of anticonvulsants)

IT **Sodium** channel
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(type IIA; electrophysiol. and pharmacol. properties of human brain type IIA Na+ channel expressed in a stable mammalian cell line in relation to effect of anticonvulsants)

IT **4368-28-9, Tetrodotoxin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(electrophysiol. and pharmacol. properties of human brain type IIA Na+ channel expressed in a stable mammalian cell line in relation to effect of anticonvulsants)

IT 57-41-0, Phenytoin 1069-66-5, **Sodium** valproate 60142-96-3, Gabapentin **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study); USES (Uses)**
(electrophysiol. and pharmacol. properties of human brain type IIA Na+ channel expressed in a stable mammalian cell line in relation to effect of anticonvulsants)

IT 7440-23-5, **Sodium**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; electrophysiol. and pharmacol. properties of human brain type IIA Na+ channel expressed in a stable mammalian cell line in relation to effect of anticonvulsants)

AN 2001:52719 CAPLUS

DN 134:338658

L62 ANSWER 5 OF 12 CAPLUS

AB . . . assays. Binding studies performed with rat brain membranes show that PNU-151774E has high affinity for binding site 2 of the **sodium** channel receptor, which is greater than that of phenytoin or lamotrigine (IC50, 8 .mu.M vs. 47 and 185 .mu.M, resp.).. . . in a use-dependent manner without modifying the first action potential in hippocampal cultured neurons. In the same prepn. PNU-151774E inhibits **tetrodotoxin**-sensitive fast **sodium** currents and high voltage-activated calcium currents under voltage-clamp conditions. These electrophysiol. activities of PNU-151774E correlate with its ability to inhibit. . . cultured mouse cortical neurons. These results suggest that PNU-151774E exerts its anticonvulsant activity, at least in part, through inhibition of **sodium** and calcium channels, stabilizing neuronal membrane excitability and inhibiting transmitter release. The possible relevance of these pharmacol. properties to its. . .

IT **Sodium** channel
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor binding; biochem. and electrophysiol. studies on mechanism of action of antiepileptic PNU-151774E)

IT 57-41-0, Phenytoin **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study); USES (Uses)**
(comparison; biochem. and electrophysiol. studies on mechanism of action of antiepileptic PNU-151774E)

IT 7440-23-5, **Sodium**, biological studies 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(current; biochem. and electrophysiol. studies on mechanism of action of antiepileptic PNU-151774E)

AN 1999:166101 CAPLUS

DN 130:332740

L62 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . 474 .mu.M, resp.) by lamotrigine. Synaptosomal uptake of noradrenaline (IC50 239 .mu.M) and dopamine (IC50 322 .mu.M) was also inhibited. **Tetrodotoxin** failed to modulate 5-HT uptake suggesting that **sodium** channel blockade does not mediate the lamotrigine effect. Lithium, **sodium** valproate, zonisamide, and carbamazepine all possess anti-manic activity but only the latter inhibited 5-HT uptake. The inhibition of the p-chloroamphetamine-induced. . .
IT 57-41-0, Phenytoin 298-46-4, Carbamazepine 1069-66-5, **Sodium** valproate **4368-28-9**, **Tetrodotoxin** 7439-93-2, Lithium, biological studies 60142-96-3, Gabapentin 68291-97-4, Zonisamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(lamotrigine inhibits monoamine uptake in vitro and modulates 5-hydroxytryptamine uptake in rats)
IT 54910-89-3, Fluoxetine **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(lamotrigine inhibits monoamine uptake in vitro and modulates 5-hydroxytryptamine uptake in rats)
AN 1998:623530 CAPLUS
DN 129:339807

L62 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . electrocorticog. was performed. The animal model was characterized by intrahippocampal perfusion with the muscarinic receptor antagonist atropine (20 mM), the **sodium** channel blocker **tetrodotoxin** (1 .mu.M) and the N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 (dizocilpine maleate, 100 .mu.M). The effectiveness of locally (600 .mu.M) or. . . all changes in extracellular transmitter levels during and after co-administration of pilocarpine. All pilocarpine-induced increases were completely prevented by simultaneous **tetrodotoxin** perfusion. Intrahippocampal administration of MK-801 and lamotrigine resulted in an elevation of hippocampal dopamine levels and protected the rats from. . .
IT 51-55-8, Atropine, biological studies **4368-28-9**, **Tetrodotoxin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA receptor-mediated pilocarpine-induced seizures and characterization in freely moving rats by microdialysis in relation to neurotransmitters of hippocampus and anticonvulsants and muscarinic receptors)
IT 77086-22-7, (+)-MK-801 **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(NMDA receptor-mediated pilocarpine-induced seizures and characterization in freely moving rats by microdialysis in relation to neurotransmitters of hippocampus and anticonvulsants and muscarinic receptors)
AN 1997:493923 CAPLUS
DN 127:203891

L62 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
TI Lamotrigine reduces voltage-gated **sodium** currents in rat central neurons in culture
AB . . . exptl. conditions designed to study voltage-gated Na+ currents. Extracellular application of LTG (10-500 .mu.M) decreased in a dose-related manner a **tetrodotoxin**-sensitive inward current that was elicited by depolarizing commands (from -80 to +20mV). The peak

amplitude of this Na+-mediated current was. . .
ST antiepileptic lamotrigine brain **sodium** channel
IT Biological transport
(antiepileptic lamotrigine reduces voltage-gated **sodium** currents in rat central neurons in culture)
IT Anticonvulsants
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiepileptic lamotrigine reduces voltage-gated **sodium** currents in rat central neurons in culture)
IT **Sodium** channel
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antiepileptic lamotrigine reduces voltage-gated **sodium** currents in rat central neurons in culture)
IT Electric potential
(biol., action; antiepileptic lamotrigine reduces voltage-gated **sodium** currents in rat central neurons in culture)
IT Brain
(cerebellum, granular layer; antiepileptic lamotrigine reduces voltage-gated **sodium** currents in rat central neurons in culture)
IT **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(antiepileptic lamotrigine reduces voltage-gated **sodium** currents in rat central neurons in culture)
AN 1997:345997 CAPLUS
DN 127:13364

L62 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . taken as the primary endpoint for neuroprotection. Compds. whose mechanism of action includes Na+-channel modulation were neuroprotective (IC50-values in .mu.M): **tetrodotoxin** 0.017, verapamil 1.18, riluzole 1.95, lamotrigine .gtoreq.10, and diphenylhydantoin 16.1. Both NMDA (MK-801 and APH) and non-NMDA (NBQX) excitatory amino. . .
ST **sodium** channel hippocampal ischemia neuroprotective drug; lubeluzole neuroprotectant hippocampal ischemia **sodium** channel
IT **Sodium** channel
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(altered Na+-channel function as in vitro model of ischemic penumbra in hippocampus and action of lubeluzole and other neuroprotective drugs)
IT Ion channel blockers
(**sodium**; altered Na+-channel function as in vitro model of ischemic penumbra in hippocampus and action of lubeluzole and other neuroprotective drugs)
IT 52-53-9, Verapamil 57-41-0, Diphenylhydantoin 66-40-0, Tetraethylammonium 1744-22-5, Riluzole 2149-70-4, N.omega.Nitro-L-arginine **4368-28-9**, **Tetrodotoxin** 10108-64-2, Cadmium chloride 42399-41-7, Diltiazem 50903-99-6, L-NAME 66085-59-4 77086-22-7, (+)-MK-801 **84057-84-1**, Lamotrigine 85797-13-3, (.+-.)-2-Amino-7-phosphonoheptanoic acid 118876-58-7, NBQX 144665-07-6, Lubeluzole 186806-31-5, R 91154 187950-02-3, R 92625
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(altered Na+-channel function as in vitro model of ischemic penumbra in hippocampus and action of lubeluzole and other neuroprotective drugs)
AN 1997:16863 CAPLUS
DN 126:207394

L62 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . corresponding to those reached in plasma or brain in exptl. animals or humans after anticonvulsant doses, presumably due to their **sodium** channel blocking properties. Microdialysis measurements of extracellular glutamate and aspartate were carried out in conscious rats in order to investigate. . . anticonvulsant compds. affected the veratridine-induced increases in extracellular glutamate or aspartate in the striatum which were, however, markedly inhibited by **tetrodotoxin** (1 .mu.M) and thus are sensitive to **sodium** channel blockade. In the cortex, the same drugs at the same doses did cause about 50% inhibition of the veratridine-induced. . .
ST anticonvulsant neurotransmitter release brain **sodium** channel; aspartate glutamate release brain anticonvulsant; carbamazepine anticonvulsant neurotransmitter release brain; lamotrigine anticonvulsant neurotransmitter release brain; oxcarbazepine anticonvulsant neurotransmitter release. . .
IT Ion channel
(**sodium**, blocking of; effects of carbamazepine, oxcarbazepine and lamotrigine on veratridine-induced aspartate and glutamate release in cortex and striatum in relation to anticonvulsant activity)
IT 7440-23-5, **Sodium**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(channels, blocking of; effects of carbamazepine, oxcarbazepine and lamotrigine on veratridine-induced aspartate and glutamate release in cortex and striatum in relation to anticonvulsant activity)
IT 298-46-4, Carbamazepine 28721-07-5, Oxcarbazepine **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study); USES (Uses)**
(effects of carbamazepine, oxcarbazepine and lamotrigine on veratridine-induced aspartate and glutamate release in cortex and striatum in relation to anticonvulsant activity)
AN 1996:498985 CAPLUS
DN 125:212415

L62 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AB . . . acceptable acid addn. salts thereof, e.g. N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea monohydrochloride or N-(2,3-dichlorophenyl)-N'-4-pyridinyl urea, and known anticonvulsant compds., e.g. ralitoline, phenytoin, lamotrigine, **tetrodotoxin**, lidocaine, and carbamazepine, are used for treating neurodegenerative disorders, perinatal asphyxia, Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral. . .
ST neurodegenerative disease pyridinyl urea compd anticonvulsant; **sodium** ion channel modulator neuroprotectant
IT Ion channel
(**sodium**, compds. modulating; neurodegenerative diseases and disorders treatment using N-(2,6-disubstituted arom.)-N'-pyridinyl ureas and other anticonvulsant compds.)
IT **4368-28-9, Tetrodotoxin 84057-84-1**, Lamotrigine 93738-40-0, Ralitoline 124421-10-9 158532-94-6
RL: THU (Therapeutic use); **BIOL (Biological study); USES (Uses)**
(neurodegenerative diseases and disorders treatment using N-(2,6-disubstituted arom.)-N'-pyridinyl ureas and other anticonvulsant compds.)
AN 1994:646337 CAPLUS
DN 121:246337

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9418972	A2	19940901	WO 1994-US1788	19940217
	WO 9418972	A3	19941222		

W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, RU, SK

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 6133299	A	20001017	US 1993-23016	19930225
AU 9462695	A1	19940914	AU 1994-62695	19940217

L62 ANSWER 12 OF 12 CAPLUS

AB . . . cultured neural circuits. The drug did not mimic diazepam as a pos. modulator of GABAA currents. In the presence of **tetrodotoxin** , voltage-gated potassium currents and composite currents evoked by L-glutamate were not significantly modulated even at the highest dose. Unitary, fast, presumptive-**sodium** spikes, evoked at low frequencies, were not blocked significantly by lamotrigine. In contrast, burst firing induced by pulsed application of. . .

IT Biological transport
(of calcium and potassium and **sodium**, in cerebral cortex neurons, lamotrigine effect on, anticonvulsant activity in relation to)

IT **84057-84-1**, Lamotrigine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological study)**; **USES (Uses)**
(anticonvulsant activity of, mechanism of, in cerebral cortex neurons, glutamate release and ion channels in)

IT 7440-09-7, Potassium, biological studies 7440-23-5, **Sodium**, biological studies 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(currents, in cerebral cortex neurons, lamotrigine effect on, anticonvulsant activity in relation to)

AN 1993:531450 CAPLUS

DN 119:131450

L85 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:202185 CAPLUS
DN 139:1308
TI Activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mechanical nociceptor sensitization
AU Parada, Carlos Amilcar; Vivancos, Gustavo Gameiro; Tambeli, Claudia Herrera; Cunha, Fernando de Queiroz; Ferreira, Sergio Henrique
CS Department of Pharmacology, Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Sao Paulo, 14049-900, Brazil
SO Proceedings of the National Academy of Sciences of the United States of America (2003), 100(5), 2923-2928
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB The present study investigated whether activation of presynaptic N-methyl-D-aspartate (NMDA) receptors in the spinal cord produces a retrograde nociceptor sensitization (hypernociception) to mech. nonnoxious stimulus. By using an electronic version of the von Frey hair test (pressure meter), s.c. intraplantar administration of prostaglandin E2 (PGE2) (50-400 ng per paw) evoked a dose-related ipsilateral paw hypernociception. In contrast, intrathecal (i.t.) administration of NMDA (5-80 ng) and PGE2 (15-150 ng) evoked dose-related bilateral paw hypernociception. The s.c. intraplantar administration of dipyrone (80-320 .mu.g per paw) or **morphine** (3 and 9 .mu.g per paw), usually used to antagonize peripheral PGE2 (100 ng per paw), induced hypernociception and also antagonized the ipsilateral (without affecting the contralateral) paw hypernociception induced by i.t. injections of NMDA (40 ng) or PGE2 (50 ng). These doses of drugs did not modify the basal mech. sensitivity of control paws. This result shows that intraspinal NMDA or PGE2 produces sensitization of the primary sensory neuron in response to mech. stimulation. In a second series of expts. it was shown that the i.t. treatment with NaV1.8 (SNS/PN3) sodium channel antisense oligodeoxynucleotides, but not mismatch oligodeoxynucleotides, decreased the mRNA expression of sodium **tetrodotoxin**-resistant channels on the dorsal root ganglia and abolished the mech. hypernociception induced by i.t. administration of NMDA. Thus, our results support the suggestion that glutamate release in the spinal cord during inflammation causes retrograde hypernociception of nociceptors assocd. with sodium tetrodotoxin-resistant channels in primary nociceptive sensory neurons.
ST presynaptic NMDA receptor PGE2 sodium channel spinal cord ganglion
IT Nerve
(C-fiber; activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA-binding; activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT Inflammation
Mechanical activation
Spinal cord
(activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)

IT **Pain**
(hypernociception; activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT Synapse
(postsynapse; activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT Nerve
(sensory, nociceptive; activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT Ganglion
(spinal; activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT 56-86-0, L-Glutamic acid, biological studies 363-24-6, Prostaglandin E2 6384-92-5, NMDA 39391-18-9, Synthetase, prostaglandin endoperoxide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
IT 57-27-2, Morphine, biological studies 68-89-3, Dipyrone
RL: PAC (Pharmacological activity); BIOL (Biological study)
(activation of presynaptic NMDA receptors coupled to NaV1.8-resistant sodium channel C-fibers causes retrograde mech. nociceptor sensitization)
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Aanonsen, L; Pain 1990, V41, P309 MEDLINE
(2) Akopian, A; Nature 1996, V379, P257 CAPLUS
(3) Bevan, S; Textbook of Pain 1999, P85
(4) Bonica, J; Hyperalgesia and Allodynia 1992, P17
(5) Dubner, R; Trends Neurosci 1992, V15, P96 CAPLUS
(6) Evans, A; J Physiol (London) 1999, V516, P163 CAPLUS
(7) Ferreira, S; Eur J Pharmacol 1978, V53, P39 CAPLUS
(8) Ferreira, S; Inflamm Res 1996, V45, P499 CAPLUS
(9) Ferreira, S; Nat New Biol 1972, V240, P200 CAPLUS
(10) Ferreira, S; Neuropharmacology 1994, V33, P1479 CAPLUS
(11) Ferreira, S; Prostaglandins 1979, V18, P191 CAPLUS
(12) Fitzgerald, E; J Physiol (London) 1999, V516, P433 CAPLUS
(13) Godfraind, T; Trends Pharmacol Sci 1995, V16, P1 CAPLUS
(14) Gold, M; Proc Natl Acad Sci USA 1996, V93, P1108 CAPLUS
(15) Gold, M; Proc Natl Acad Sci USA 1999, V96, P7645 CAPLUS
(16) Haley, J; Hyperalgesia and Allodynia 1992, P281
(17) Handwerker, H; Hyperalgesia and Allodynia 1992, P107
(18) Herrero, I; Nature 1992, V360, P163 CAPLUS
(19) Jaffe, D; J Neurophysiol 1994, V72, P471 CAPLUS
(20) Johenning, F; J Neurosci 2002, V22, P5344 CAPLUS
(21) Khasar, S; Neurosci Lett 1998, V256, P17 CAPLUS
(22) Kuba, K; J Physiol (London) 1980, V298, P251 CAPLUS
(23) Lamotte, R; Hyperalgesia and Allodynia 1992, P175
(24) Liu, H; Nature 1997, V386, P721 CAPLUS
(25) Liu, H; Proc Natl Acad Sci USA 1994, V91, P8383 CAPLUS
(26) Lorenzetti, B; Eur J Pharmacol 1985, V114, P375 CAPLUS
(27) Lynn, B; Textbook of Pain 1984, P19
(28) Malmberg, A; Science 1992, V257, P1276 CAPLUS
(29) Millan, M; Prog Neurobiol 1999, V57, P1 CAPLUS
(30) Minami, T; Brain Res 2001, V895, P178 CAPLUS
(31) Minami, T; Pain 1994, V57, P225 CAPLUS
(32) Moller, K; J Neurosci Methods 1998, V84, P41 MEDLINE
(33) Moncada, S; Inflammation 1978, P588 CAPLUS
(34) Papir-Kricheli, D; Pain 1987, V31, P263 CAPLUS
(35) Rizzuto, R; Curr Opin Neurobiol 2001, V11, P306 CAPLUS

(36) Roberts, L; Goodman & Gilman's: The Pharmacological Basis of Therapeutics 2001, P687
(37) Rodrigues, A; Br J Pharmacol 2000, V129, P110 CAPLUS
(38) Schermerhorn, T; Cell Calcium 2000, V27, P163 CAPLUS
(39) Soares, A; Eur J Pharmacol 2000, V400, P67 CAPLUS
(40) Tanaka, M; NeuroReport 1998, V9, P967 CAPLUS
(41) Urban, M; Proc Natl Acad Sci USA 1999, V96, P7687 CAPLUS
(42) Usachev, Y; BioEssays 1999, V21, P743 MEDLINE
(43) Waxman, S; Proc Natl Acad Sci USA 1999, V96, P7635 CAPLUS
(44) Wilcox, G; IASP: Refresher Courses on Pain Management--An Updated Review (Refresher Course Syllabus) 1999, P572
(45) Woolf, C; Curr Opin Neurobiol 1994, V4, P525 MEDLINE
(46) Zhang, H; Nat Biotechnol 2000, V18, P862 CAPLUS

L85 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:567344 CAPLUS
DN 138:147553
TI Morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa
AU Moran, Timothy D.; Smith, Peter A.
CS University Centre for Neuroscience and Department of Pharmacology, University of Alberta, Edmonton, AB, Can.
SO Journal of Pharmacology and Experimental Therapeutics (2002), 302(2), 568-576
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
CC 1-11 (Pharmacology)
AB High doses of intrathecally applied morphine or morphine-3.beta.-D-glucuronide (M3G) produce allodynia and hyperalgesia. Whole-cell patch-clamp recordings were made from substantia gelatinosa neurons in transverse slices of adult rat lumbar spinal cord to compare the actions of M3G with those of the .mu.-opioid agonist, DAMGO ([D-Ala2,N-Met-Phe4,Gly-ol5]-enkephalin), and the ORL1 agonist, nociceptin/orphanin FQ (N/OFQ). M3G (1-100 .mu.M) had little or no effect on evoked excitatory postsynaptic currents (EPSC) and no effect on postsynaptic membrane conductance. In contrast, 1 .mu.M DAMGO and 1 .mu.M N/OFQ reduced the amplitude of evoked EPSCs and activated an inwardly rectifying K+ conductance. M3G did not attenuate the effect of DAMGO or N/OFQ on evoked EPSC amplitude. However, 1 to 100 .mu.M M3G reduced the amplitude of evoked GABAergic and glycinergic inhibitory postsynaptic current (IPSC) by up to 48%. This effect was naloxone-insensitive. The evoked IPSC was also attenuated by DAMGO, but not by N/OFQ. Because M3G reduced the frequency of **tetrodotoxin**-insensitive miniature IPSCs and increased paired-pulse facilitation, it appeared to act presynaptically to disinhibit substantia gelatinosa neurons. This effect, which does not appear to involve .mu.-opioid or ORL1 receptors, may contribute to the allodynia and hyperalgesia obsd. after intrathecal application of high doses of **morphine**.
ST morphine glucuronide inhibitory synaptic transmission substantia gelatinosa
IT Brain
   (GABAergic system; morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
   (ORL1 (opioid receptor-like 1); morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT **Pain**
Skin, disease
   (allodynia; morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)

IT **Pain**
(hyperalgesia; morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT Analgesics
(morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT Neurotransmission
(postsynaptic inhibitory; morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT Brain
(substantia gelatinosa; morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT Neurotransmission
(synaptic; morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT 78123-71-4, DAMGO 170713-75-4, Nociceptin
RL: PAC (Pharmacological activity); BIOL (Biological study)
(morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
IT 20290-09-9, Morphine-3-glucuronide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(morphine-3.beta.-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa)
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ahmadi, S; Mol Pharmacol 2001, V59, P612 CAPLUS
(2) Bartlett, S; Life Sci 1996, V58, P447 MEDLINE
(3) Bartlett, S; Pharmacol Toxicol 1994, V75, P73 CAPLUS
(4) Beyer, C; Life Sci 1985, V37, P875 CAPLUS
(5) Boerner, U; Drug Metab Rev 1975, V4, P39 CAPLUS
(6) Christrup, L; Acta Anaesthesiol Scand 1997, V41, P116 CAPLUS
(7) de Conno, F; Pain 1991, V47, P337 MEDLINE
(8) Frances, B; J Pharmacol Exp Ther 1992, V262, P25 CAPLUS
(9) Glaum, S; J Neurosci 1994, V14, P4965 CAPLUS
(10) Goucke, C; Pain 1994, V56, P145 MEDLINE
(11) Grudt, T; J Neurosci 1994, V14, P1646 CAPLUS
(12) Grudt, T; J Physiol (Lond) 1998, V507, P473 CAPLUS
(13) Hagen, N; J Pain Symptom Manage 1997, V14, P51 MEDLINE
(14) Halliday, A; Life Sci 1999, V65, P225 CAPLUS
(15) Heger, S; Br Med J 1999, V319, P627 MEDLINE
(16) Hewett, K; Pain 1993, V53, P59 CAPLUS
(17) Jennings, E; Neuroreport 2001, V12, P645 CAPLUS
(18) Kaneko, M; J Pharmacol Exp Ther 1997, V282, P928 CAPLUS
(19) Kohno, T; J Physiol (Lond) 1999, V518, P803 CAPLUS
(20) Lai, C; Neuroscience 1997, V81, P887 CAPLUS
(21) Lambert, D; Biochem Pharmacol 1993, V46, P1145 CAPLUS
(22) Liebel, J; Br J Pharmacol 1997, V121, P425 CAPLUS
(23) Loser, S; Naunyn-Schmiedeberg's Arch Pharmacol 1996, V354, P192 MEDLINE
(24) Meunier, J; Nature (Lond) 1995, V377, P532 CAPLUS
(25) Moran, T; Soc Neurosci Abstr 2000, V26, P623.6
(26) Osborne, P; Br J Pharmacol 2000, V131, P1422 CAPLUS
(27) Pasternak, G; Life Sci 1987, V41, P2845 CAPLUS
(28) Paul, D; J Pharmacol Exp Ther 1989, V251, P477 CAPLUS
(29) Reinscheid, R; Science (Wash DC) 1995, V270, P792 CAPLUS
(30) Schneider, S; J Neurophysiol 1998, V80, P2954 CAPLUS
(31) Sjogren, P; Acta Anaesthesiol Scand 1998, V42, P1070 MEDLINE
(32) Sjogren, P; Pain 1993, V55, P93 MEDLINE
(33) Sjogren, P; Pain 1994, V59, P313 MEDLINE
(34) Smith, M; Life Sci 1990, V47, P579 CAPLUS
(35) Sullivan, A; Brain Res 1989, V482, P219 CAPLUS
(36) Woolf, C; Brain Res 1981, V209, P491 CAPLUS
(37) Xu, I; Neuroreport 1999, V10, P3681 CAPLUS
(38) Yaksh, T; Anesthesiology 1986, V64, P590 CAPLUS

(39) Yaksh, T; J Pharmacol Exp Ther 1988, V244, P501 CAPLUS
(40) Zeilhofer, H; J Neurosci 2000, V20, P4922 CAPLUS
(41) Zhang, Z; Pain 2001, V92, P351 CAPLUS

L85 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:428064 CAPLUS
DN 136:257039
TI Vincristine-induced allodynia in the rat
AU Nozaki-Taguchi, N.; Chaplan, S. R.; Higuera, E. S.; Ajakwe, R. C.; Yaksh, T. L.
CS Department of Anesthesiology 0818, Anesthesiology Research Laboratory, University of California, San Diego, La Jolla, CA, 92093-0818, USA
SO Pain (2001), 93(1), 69-76
CODEN: PAINDB; ISSN: 0304-3959
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-11 (Pharmacology)
AB The aims of this study were two-fold: first, to simplify the method for creating a recently described neuropathic **pain** model in the rat, and second, to evaluate the effects of a no. of drugs with analgesic or antihyperalgesic properties, in this model. Continuous i.v. vincristine infusion (1-100 .mu.g kg-1 day -1) for 14 days resulted in a dose-dependent tactile allodynia (as measured by von Frey filaments) by 7 days at doses between 30-100.mu.g kg-1 day -1, with a hindlimb motor deficit obsd. at doses greater than 50 .mu.g kg-1 day -1. No thermal hyperalgesia was obsd. Systemic **morphine**, lidocaine, mexiletine and pregabalin (given i.p.) produced significant redn. of the allodynia, while **tetrodotoxin** was without effect. Continuous i.v. infusion of vincristine in rats thus provides a reliable model of chemotherapy-induced neuropathy which may be used in defining the mechanism and pharmacol. of this clin. relevant condition.
ST vincristine allodynia neuropathy analgesic
IT **Pain**
Skin, disease
(allodynia; vincristine-induced allodynia in the rat and pharmacol. of analgesics)
IT Nerve, disease
(neuropathy; vincristine-induced allodynia in the rat and pharmacol. of analgesics)
IT Analgesics
(vincristine-induced allodynia in the rat and pharmacol. of analgesics)
IT 57-22-7, Vincristine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(vincristine-induced allodynia in the rat and pharmacol. of analgesics)
IT 57-27-2, Morphine, biological studies 137-58-6, Lidocaine 31828-71-4, Mexiletine 148553-50-8, Pregabalin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vincristine-induced allodynia in the rat and pharmacol. of analgesics)
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Akopian, A; Nature 1996, V379, P257 CAPLUS
(2) Aley, K; Neuroscience 1996, V73, P259 CAPLUS
(3) Ashburn, M; Anesth Analg 1993, V76, P402 MEDLINE
(4) Authier, N; NeuroReport 1999, V10, P965 CAPLUS
(5) Boucher, T; Science 2000, V290, P124 CAPLUS
(6) Burns, B; J Laryngol Otol 1998, V112, P485 MEDLINE
(7) Calabresi, P; Goodman and Gilman's the pharmacological basis of therapeutics 1990, P1236
(8) Calcutt, N; Br J Pharmacol 1997, V122, P1478 CAPLUS
(9) Cavaletti, G; Cancer 1995, V75, P1141 MEDLINE
(10) Chabal, C; Anesthesiology 1992, V76, P513 MEDLINE
(11) Chaplan, S; J Pharmacol Exp Ther 1997, V280, P829 CAPLUS

(12) Dejgard, A; Lancet 1988, V1, P9 MEDLINE
(13) Dib-Hajj, S; Proc Natl Acad Sci 1998, V95, P8963 CAPLUS
(14) Dumontet, C; J Clin Oncol 1999, V17, P1061 CAPLUS
(15) Forman, A; Oncology 1990, V4, P57 MEDLINE
(16) Forman, A; Oncology 1990, V4, P85 MEDLINE
(17) Forman, A; published erratum appears in Oncology 1990, V4(4), P16
(18) Kastrup, J; Br Med J 1986, V292, P173 MEDLINE
(19) Lee, Y; Neurosci Lett 1995, V199, P111 CAPLUS
(20) Luo, Z; J Neurosci in press 2001
(21) Lyu, Y; Brain Res 2000, V871, P98 CAPLUS
(22) McQuay, H; Br Med J 1995, V311, P1047 CAPLUS
(23) Portenoy, R; Pain 1990, V43, P273 MEDLINE
(24) Postma, T; J Neurooncol 1993, V15, P23 MEDLINE
(25) Rogart, R; Proc Natl Acad Sci 1989, V86, P8170 CAPLUS
(26) Sangameswaran, L; J Biol Chem 1996, V271, P5953 CAPLUS
(27) Tanner, K; J Comp Neurol 1998, V395, P481 CAPLUS
(28) Tanner, K; J Neurosci 1998, V18, P6480 CAPLUS
(29) Tate, S; Nat Neurosci 1998, V1, P653 CAPLUS
(30) Taylor, C; Epilepsy Res 1998, V29, P233 CAPLUS
(31) Thomas, P; Rev Mal Respir 1993, V10, P268 MEDLINE
(32) Topp, K; J Comp Neurol 2000, V424, P563 CAPLUS
(33) Tyndel, F; Lancet 1994, V343, P1363 MEDLINE
(34) Wahren, L; Pain 1991, V46, P23 MEDLINE
(35) Waxman, S; Muscle Nerve 1999, V22, P1177 CAPLUS

L85 ANSWER 4 OF 10 CAPLUS
AN 2000:619179 CAPLUS
DN 133:344510
TI Opposite modulation of histaminergic neurons by nociceptin and morphine
AU Eriksson, K. S.; Stevens, D. R.; Haas, H. L.
CS Department of Physiology II, Heinrich-Heine-Universitat, Dusseldorf, D-40225, Germany
SO Neuropharmacology (2000), 39(12), 2492-2498
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-11 (Pharmacology)
AB We have studied the effects of nociceptin/orphanin FQ on the histaminergic neurons in the tuberomammillary (TM) nucleus and compared them with the actions of opioid agonists. Intracellular recordings of the membrane potential were made with sharp electrodes from superfused rat hypothalamic slices. Nociceptin strongly inhibited the firing of the TM neurons. In the concn. range 10-300 nM, nociceptin hyperpolarized the neurons in a dose-dependent and reversible manner. Insensitivity to **tetrodotoxin** indicated a postsynaptic effect which was assocd. with decreased input resistance. Voltage-current plots suggested the involvement of a potassium conductance which was highly sensitive to Ba2+ and decreased by Cs+, in keeping with the activation of an inwardly rectifying potassium channel. **Morphine** (20-100 .mu.M) depolarized the TM neurons and increased their firing, and this effect was blocked by **tetrodotoxin**. Dynorphin A(1-13) at 100-300 nM did not affect the TM neurons. Nociceptin and **morphine** modulate the activity of the TM neurons, and most likely histamine release, in opposite ways. Histamine has an antinociceptive effect in the brain and may be involved in opioid-induced analgesia. Nociceptin might therefore influence **pain** transmission by inhibiting opioid-induced histamine release from the TM nucleus and also modulate other physiol. mechanisms which have been ascribed to the histaminergic system.
ST nociceptin morphine analgesic hypothalamus histaminergic neuron
IT Brain
(histaminic system; opposite modulation of histaminergic neurons by nociceptin and morphine)
IT Nervous system

(histaminic; opposite modulation of histaminergic neurons by nociceptin and morphine)

IT Analgesics
(opposite modulation of histaminergic neurons by nociceptin and morphine)

IT Brain
(tuberomamillary nucleus; opposite modulation of histaminergic neurons by nociceptin and morphine)

IT 57-27-2, Morphine, biological studies 170713-75-4, Nociceptin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opposite modulation of histaminergic neurons by nociceptin and morphine)

IT 51-45-6, Histamine, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(opposite modulation of histaminergic neurons by nociceptin and morphine)

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Barke, K; Journal of Neurochemistry 1994, V63, P238 CAPLUS
(2) Bunzow, J; FEBS Letters 1994, V347, P284 CAPLUS
(3) Chikai, T; Journal of Neurochemistry 1994, V62, P724 CAPLUS
(4) Chikai, T; Neuroscience Letters 1995, V196, P137 CAPLUS
(5) Connor, M; British Journal of Pharmacology 1996, V119, P1614 CAPLUS
(6) Darland, T; Trends in Neuroscience 1998, V21, P215 CAPLUS
(7) Di-Chiara, G; The Journal of Pharmacology and Experimental Theraputics 1988, V244, P1067 CAPLUS
(8) Diewald, L; European Journal of Neuroscience 1997, V9, P2406 MEDLINE
(9) Gifford, A; Brain Research 1994, V638, P325 CAPLUS
(10) Glick, S; Nature 1978, V273, P547 CAPLUS
(11) Gulat-Marnay, C; Jounal of Neurochemistry 1990, V55, P47 CAPLUS
(12) Haas, H; Journal of Physiology 1988, V399, P633 CAPLUS
(13) Haas, H; Nature 1983, V302, P432 CAPLUS
(14) Hough, L; European Journal of Pharmacology 1992, V215, P69 CAPLUS
(15) Hough, L; Life Sciences 1999, V64, PPL79 CAPLUS
(16) Jenck, F; Proceedings of the National Academy of Science, USA 1997, V94, P14854 CAPLUS
(17) Johnson, S; Journal of Neuroscience 1992, V12, P483 CAPLUS
(18) Knoflach, F; Journal of Neuroscience 1996, V16, P6657 CAPLUS
(19) Leurs, R; Trends in Pharmacological Sciences 1998, V19, P177 CAPLUS
(20) Leventhal, L; European Journal of Pharmacology 1998, V349, PR1 CAPLUS
(21) Li, B; The Journal of Pharmacology and Experimental Theraputics 1996, V276, P500 CAPLUS
(22) Malmberg-Aiello, P; British Journal of Pharmacology 1994, V111, P1269 CAPLUS
(23) Malmberg-Aiello, P; Naunyn-Schmiedeberg's Archive of Pharmacology 1997, V355, P354 CAPLUS
(24) Mansour, A; Journal of Comparative Neurology 1994, V350, P412 CAPLUS
(25) Meunier, J; Nature 1995, V377, P532 CAPLUS
(26) Murphy, N; Neuroscience 1996, V75, P1 CAPLUS
(27) Neal, C; Journal of Comparative Neurology 1999, V406, P503 CAPLUS
(28) Onodera, K; Progress in Neurobiology 1994, V42, P685 CAPLUS
(29) Panula, P; Neuroscience 1989, V28, P585 MEDLINE
(30) Panula, P; Proceedings of the National Academy of Science, USA 1984, V81, P2572 CAPLUS
(31) Peluso, J; Journal of Neuroimmunology 1998, V81, P184 CAPLUS
(32) Privou, C; Neuropharmacology 1998, V37, P1019 CAPLUS
(33) Quigley, D; Peptides 1998, V19, P133 CAPLUS
(34) Reinsheid, R; Science 1995, V270, P792
(35) Sakata, T; Physiology and Behavior 1988, V44, P539 CAPLUS
(36) Schwartz, J; Physiological Reviews 1991, V71, P1 CAPLUS
(37) Shimokawa, A; Neuroscience Letters 1998, V244, P21 CAPLUS

(38) Stevens, D; European Journal of Neuroscience 1999, V11, P1148 MEDLINE
(39) Stevens, D; Journal of Physiology (London) 1996, V493, P747 CAPLUS
(40) Thoburn, K; Pain 1994, V58, P29 CAPLUS
(41) Vaughan, C; British Journal of Pharmacology 1996, V117, P1609 CAPLUS
(42) Vaughan, C; Journal of Neuroscience 1997, V17, P996 CAPLUS
(43) Vaughan, C; Nature 1997, V390, P611 CAPLUS
(44) Vorobjev, V; Neuron 1993, V11, P837 CAPLUS
(45) Wada, H; Trends in Neuroscience 1991, V14, P415 MEDLINE
(46) Wagner, E; Neuroendocrinology 1998, V67, P73 CAPLUS
(47) Wick, M; Molecular Brain Research 1994, V27, P37 CAPLUS

L85 ANSWER 5 OF 10 CAPLUS
AN 1995:988766 CAPLUS
DN 124:22504
TI Simultaneous activation of spinal antiopioid system (neuropeptide FF) and **pain** facilitatory circuitry by stimulation of opioid receptors in rats
AU Devillers, Jean-Philippe; Boisserie, Frederic; Laulin, Jean-Paul; Larcher, Agnes; Simonnet, Guy
CS INSERM U. 259, Universite de Bordeaux II, Laboratoire de Psychobiologie des comportements adaptatifs, 1 rue Camille Saint-Saeens, Bordeaux, 33077, Fr.
SO Brain Research (1995), 700(1,2), 173-81
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Neuropeptide FF (NPFF) is a mammalian FMRFamide-like octapeptide with antiopioid properties that inhibits morphine-induced analgesia but also produces hyperalgesia. In the present study, a series of three expts. was carried out to investigate the interactions between opioid receptor stimulation and antiopioid systems. First, by using an in vitro superfusion system with rat spinal cord slices, the authors showed that **morphine** stimulated NPFF release in a dose-dependent manner. The stimulating effect which was obsd. with **morphine** concns. as low as 100 fM reached a max. at 0.1 nM, then decreased and was ineffective at 10 .mu.M. The **morphine**-induced release of NPFF was abolished by naloxone (1 .mu.M) but unaltered by **tetrodotoxin**. Second, by an in vivo approach, the authors showed that a single heroin administration (2.5 mg/kg, s.c.) elicited in 30 min a drastic drop (38%) in spinal NPFF content. In a third expt., the authors evaluated the capacity of naloxone in revealing an antiopioid component assocd. with opioid receptor stimulation. The administration of naloxone (1 mg/kg, s.c.) 25 min following that of heroin (2.5 mg/kg, s.c.), not only abolished the heroin-induced increase of tail-flick latency, but also lowered it under the basal value by 30%. These results indicate that opioid receptor stimulation activates both **pain** inhibitory and **pain** facilitatory systems in which NPFF may play a significant role and that opiate-induced analgesia is always partly masked.
ST spinal neuropeptide FF **pain** circuitry
IT **Pain**
Spinal cord
(simultaneous activation of spinal antiopioid system (neuropeptide FF) and **pain** facilitatory circuitry by stimulation of opioid receptors in rats)
IT Opioid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(simultaneous activation of spinal antiopioid system (neuropeptide FF) and **pain** facilitatory circuitry by stimulation of opioid receptors in rats)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(opioid, simultaneous activation of spinal antiopioid system (neuropeptide FF) and **pain** facilitatory circuitry by stimulation of opioid receptors in rats)

IT 57-27-2, Morphine, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(simultaneous activation of spinal antiopioid system (neuropeptide FF) and **pain** facilitatory circuitry by stimulation of opioid receptors in rats)

IT 99566-27-5, Neuropeptide FF
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(simultaneous activation of spinal antiopioid system (neuropeptide FF) and **pain** facilitatory circuitry by stimulation of opioid receptors in rats)

L85 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1995:556877 CAPLUS

DN 122:282695

TI Opioidergic inhibition of capsaicin-evoked release of glutamate from rat spinal dorsal horn slices

AU Ueda, M.; Sugimoto, K.; Oyama, T.; Kuraishi, Y.; Satoh, M.

CS Faculty Pharmaceutical Sciences, Kyoto Univ., Kyoto, 606-01, Japan

SO Neuropharmacology (1995), 34(3), 303-8
CODEN: NEPHBW; ISSN: 0028-3908

PB Elsevier

DT Journal

LA English

CC 2-5 (Mammalian Hormones)

AB The authors investigated the effects of opioid agonists on the capsaicin-evoked release of glutamate from nociceptive primary afferent fibers of the rat (6-8 wk) using a fluorometric online continuous monitoring system for glutamate. In the presence of 0.3 .mu.M **tetrodotoxin**, the application of 3 .mu.M capsaicin to spinal dorsal horn slices produced an evoked glutamate release (55.9 pmol.cntdot.mg-1 protein). DAMGO ([D-Ala2,N-Me-Phe4,Gly5-ol]enkephalin; 0.3-10 .mu.M) and **morphine** (1-30 .mu.M), .mu.-opioid agonists, produced a concn.-dependent redn. (.apprx.85 and .apprx.77% redn., resp.) in the capsaicin (3 .mu.M)-evoked release of glutamate. These inhibitory effects were significantly antagonized by naloxone (1 .mu.M). DPDPE ([D-Pen2,5]enkephalin; 1-10 .mu.M), a .delta.-opioid agonist, also reduced the capsaicin-evoked release in a concn.-dependent manner (.apprx.59% redn.). Naltrindole (1 .mu.M), a selective .delta.-antagonist, significantly antagonized the inhibitor effect of DPDPE (10 .mu.M). In contrast, neither U-50,488H (1-10 .mu.M) nor U-69,593 (10 .mu.M), .kappa.-opioid agonists, had any effects on the evoked release of glutamate. These results suggest that .mu.-, and .delta.-opioid agonists modulate **pain** transmission in the spinal dorsal horn, at least in part, by inhibiting the release of glutamate from capsaicin-sensitive primary afferents.

ST opioid capsaicin glutamate release spinal neuron; **pain** transmission spinal cord glutamate opioid

IT Neurotransmission
(opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT Spinal cord
(dorsal horn, opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT Nerve
(primary sensory, nociceptive; opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by

inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT Opioid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.delta.-, opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.delta.-opioid, opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT Opioid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.mu.-, opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.mu.-opioid, opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT 56-86-0, Glutamic acid, biological studies 404-86-4, Capsaicin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

IT 57-27-2, Morphine, biological studies 78123-71-4, DAMGO 88373-73-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(opioid agonists modulation of **pain** transmission in the spinal dorsal horn mediation by inhibition of glutamate release from capsaicin-sensitive primary afferents.)

L85 ANSWER 7 OF 10 CAPLUS

AN 1995:480857 CAPLUS

DN 122:256105

TI Subanesthetic concentrations of lidocaine selectively inhibit a nociceptive response in the isolated rat spinal cord

AU Jaffe, Richard A.; Rowe, Michael A.

CS Department Anesthesia, Stanford University School Medicine, Stanford, CA, 94305, USA

SO Pain (1995), 60(2), 167-74
CODEN: PAINDB; ISSN: 0304-3959

DT Journal

LA English

CC 1-11 (Pharmacology)

AB Systemically administered local anesthetics are known to provide analgesia in a variety of **pain** states; however, the site of action and the mechanism by which these effects are produced remain in question. In the present study, the effects of low (subblocking for nerve conduction) concns. of lidocaine on a spinal cord nociceptive potential were studied. Spinal cords were removed from neonatal rats and maintained in vitro. Lumbar dorsal and ipsilateral ventral roots were attached to suction electrodes for stimulation and recording, resp. Following a stabilization period (60-120 min) with control measurements, each prepn. was exposed to a single concn. of lidocaine (30-60 min) then returned to control perfusate for recovery (60-120 min). Data were digitized and integrals

computed for both monosynaptic and slow ventral root potentials (VRP). Low concns. of lidocaine produced a selective redn. in the magnitude of the slow-VRP. At lidocaine concns. of 1-10 .mu.g/mL (3.6-36 .mu.M), the slow-VRP was reduced from 79% to 36% of control. Recovery to pre-exposure control levels was slow and sometimes not complete after 60-120 min in drug-free perfusate. The monosynaptic component of the VRP was unaffected by lidocaine at any concn., suggesting that the depression of the slow-VRP cannot be attributed to simple conduction block. The addn. of naloxone 0.1 .mu.M to the perfusate had minimal effect on lidocaine-induced depression. Although resembling the selective effects of **morphine**, the antinociceptive effects of lidocaine do not appear to be primarily mediated through opiate receptors. Subblocking concns. of **tetrodotoxin**, a selective sodium-channel blocker, did not mimic the effects of lidocaine. However, a subblocking concn. of benzonatate, an orally effective local anesthetic, did produce lidocaine-like selective effects on the slow-VRP. This study demonstrated that lidocaine at clin. relevant concns. can selectively depress a well-characterized nociceptive response in the isolated rat spinal cord. It is proposed that the site of action for systemic lidocaine analgesia is, at least in part, at the level of the spinal cord.

ST local anesthetic analgesic spinal cord; benzonatate lidocaine analgesic spinal cord

IT Analgesics
Spinal cord
(analgesic effects of systemic local anesthetics mediated through spinal cord)

IT Anesthetics
(local, analgesic effects of systemic local anesthetics mediated through spinal cord)

IT 104-31-4, Benzonatate 137-58-6, Lidocaine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic effects of systemic local anesthetics mediated through spinal cord)

L85 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1984:204156 CAPLUS
DN 100:204156
TI Sensory neural mechanisms in contraction of the rabbit isolated sphincter pupillae: analysis of the responses to capsaicin and electrical field stimulation
AU Zhang, S. Q.; Butler, J. M.; Cole, D. F.
CS Inst. Ophthalmol., London, WC1H 9QS, UK
SO Experimental Eye Research (1984), 38(2), 153-63
CODEN: EXERA6; ISSN: 0014-4835
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB Elec. field stimulation produced contractions of the rabbit isolated iris sphincter muscle which were completely blocked by tetrodotoxin (10-6M). Low-frequency (0.16-5 Hz) responses were atropine resistant, but were prevented by sensory (trigeminal) denervation, and were considered to be due to antidromic stimulation of sensory nerves. Higher-frequency (10-40 Hz) responses were apparently unaffected by atropine alone (3 .times. 10-7M) and unaltered by sensory denervation, but were completely blocked by a combination of both. Thus, at higher frequencies, both cholinergic and sensory nerves would seem to be activated. Capsaicin [404-86-4]-induced contraction of the isolated iris sphincter muscle, previously shown to be dependent upon an intact and functional sensory nerve supply, was not suppressed by atropine (3 .times. 10-7M) or by **tetrodotoxin** (10-6M). Capsaicin therefore, although acting via sensory nerves, does not seem to require axonal conduction of Na+ flux to produce a response. This **pain**-producing substance may therefore

act directly on sensory elements to release a mediator without requiring excitation of adjacent fibers by axon reflex. Contractile responses to capsaicin and also to low-frequency elec. stimulation were partially inhibited by **morphine** [57-27-2] (5 .times. 10-5M), which in contrast had no effect on responses to carbachol [51-83-2] or to substance P [33507-63-0]. Thus, at the peripheral as at the central endings of these bipolar primary afferent fibers, morphine may inhibit the release of the putative mediator.

ST eye iris sphincter neurotransmission

IT Neuromuscular transmission
(by eye iris sphincter, capsaicin in relation to)

IT Eye
(iris sphincter, neuromuscular transmission by, capsaicin in relation to)

IT Nerve center and Ganglion
(trigeminal, eye iris sphincter neuromuscular transmission regulation by, capsaicin in relation to)

IT 51-83-2 57-27-2, biological studies 404-86-4 33507-63-0
RL: BIOL (Biological study)
(eye iris sphincter neuromuscular transmission in relation to)

=> d 9-10 hit, ibib

L85 ANSWER 9 OF 10 USPATFULL on STN

AB This invention relates to a method of producing analgesia in a mammal experiencing **pain** by systemically administering an effective amount of a composition comprising essentially of a sodium channel blocking compound, in a suitable pharmaceutical vehicle, to alleviate the **pain**.

SUMM This invention presents a method of alleviating **pain**, such as central **pain**, **pain** arising from cancer and phantom limb **pain**, by systemic administration of sodium channel blocking compounds, including tetrodotoxin and saxitoxin.

SUMM **Pain** is a sensation that hurts. It may cause discomfort or distress or agony. It may be steady or throbbing. It may be stabbing, aching, or pinching. However **pain** is felt, only the person experiencing **pain** can describe it or define it. Because **pain** is so individual, **pain** cannot be truly evaluated by any third person.

SUMM The World Health Organization (WHO) recognizes a "Three-step Analgesic Ladder" for pharmacologic management of **pain**. The ladder begins with relatively low doses of low-potency analgesics and progresses to higher doses of more potent compounds. The three steps involve use of:

SUMM Lower-potency opioids with or without coanalgesics as **pain** persists or increases to moderate levels;

SUMM High-potency opioids with or without nonopioid coanalgesics as **pain** persists or increases to severe levels.

SUMM Use of opioid analgesics, even for treatment of severe **pain**, is controversial in the medical community, due to the possibility of addiction. See, e.g. S. E. Weitz et al., New Jersey Medicine, Vol. 97: 63-67 (2000).

SUMM Pan et al., U.S. Pat. No. 5,846,975, discloses the use of amino hydrogenated quinazoline compounds, such as **tetrodotoxin**, for treating drug dependence in humans. **Tetrodotoxin** was shown to be effective against withdrawal symptoms from opium, heroin, **morphine**, cocaine, amphetamine, dolandin, dihydroetorphine and

methadone. Amounts effective for relieving withdrawal symptoms are described in this patent.

SUMM U.S. Pat. No. 6,030,974 describes a method of producing local anesthesia in a mammal experiencing **pain** in an epithelial tissue region. The method includes topically administering to the region, in a suitable pharmaceutical vehicle, an effective dose of a long-acting sodium channel blocking compound. The sodium channel blocking compound of U.S. Pat. No. 6,030,974 can be a formulation of tetrodotoxin or saxitoxin at a concentration of between 0.001-10 mM.

SUMM Zapata et al., **Pain** 72:41-49 (1997) discusses the utilization of tetrodotoxin for the inhibition of neuropathic ectopic activity in neuromas, dorsal root ganglia and dorsal horn neurons. The neuronal activity arises from neuroma caused by mechanical, chemical or ischemic injury. The effect of intravenously administered TTX on the neuronal induction by sciatic nerves in male rats was researched. However, the dosages and effects studied by Zapata et al. were applied to animals under anesthesia and artificial ventilation, thus these doses are above the maximal tolerated dose and the administration was under conditions that are not applicable to the presently intended clinical use of tetrodotoxin.

SUMM Although there has been extensive research into the effectiveness of TTX and its derivatives as a sodium channel blocker and local anesthetic, systemic administration of pure TTX as an analgesic has never been disclosed. The potential for TTX to alleviate **pain** arising from the activity in the central nervous system, rather from the stimulation of peripheral nerves does not seem to have been described.

SUMM The alleviation of chronic severe **pain**, such as that arising from cancer and "phantom limb **pain**" is an important topic in modern medicine. Cancer is highly pervasive in the human population.

SUMM A person suffering from cancer frequently experiences severe **pain**. This **pain** can also be known as central **pain** or chronic **pain**. However, a patient need not be suffering from cancer to experience central **pain** or chronic **pain**. A related type of **pain** is phantom limb **pain**. These types of **pain** have been treated by opiates such as morphine. A drawback of the opiate analgesia is the addictive nature of the opiates.

SUMM Acute local **pain** can arise, for example, from toothaches, eye irritation, inflammation in a nervous tissue region, canker sores, genital ulcers, and **pain** in epithelial tissues caused by burns, surgery or soreness.

SUMM Perception of **pain** can also be divided into three areas; acute nociceptive processing, facilitated **pain** arising from persistent afferent input (as after tissue injury) and neuropathic **pain** that arises from altered processing after nerve injury.

SUMM Some sodium channel blocking compounds, e.g. lidocaine and mexiletine, typically used as local anesthetics, have also been administered systemically. These compounds seem to be marginally effective in blocking acute nociceptive processing, and there is some effect observable upon spinal processing and substance P release, indicating effects on facilitated **pain**. However, the effective doses are above the maximum tolerated dose and thus side effects have precluded use of these compounds as systemic analgesics. Furthermore, sodium channel blockers have previously been found entirely ineffective in managing neuropathic **pain**. See, M. S. Wallace, "Calcium and Sodium channel blocking compounds for the Treatment of **Pain**",

Clin. J. **Pain**, Vol. 16: S80-S85 (2000).

SUMM Several sodium channel blockers such as lidocaine and carbamazepine have been used in the treatment of neuropathic **pain** and trigeminal neuralgia. These substances may block sodium channels to abolish abnormal peripheral nerves activity at concentrations which do not block nerve conduction. Since it may cause severe damage to the function of liver, however, carbamazepine should be restricted from being used on women in the early stage of pregnancy and during breasting period, and should be used with caution on older people and those who have glaucoma or severe angiocardiopathy. On the other hand, lidocaine has such an excitation effect on the central nerve system that it can cause tremor, shivering and clonic spasm. Therefore, these two drugs are considered inappropriate to promote as new analgesics for systemic use. This has stimulated interest in developing other sodium channel blocking drugs.

SUMM In 1998, Rabert et al demonstrated that the existence of more than one type of sodium channels in rat dorsal root ganglion (DRG) sensory neurons. These sodium channels have been distinguished on the basis of a differential sensitivity to TTX: a TTX-sensitive sodium channel (TTX-S) is blocked by TTX with IC.sub.50 of 1-20 nM. A TTX-resistant sodium channel (TTX-R) is blocked by TTX with an IC.sub.50 of .about.100 .mu.M. The rBIIA, rBII1, rSKM1, rPN1 and rPN4 sodium channels are all TTX-S, whereas rPN3/SNS sodium channels are TTX-R. There are also two types of sodium channels in human DRG sensory neurons: hPN1 is a TTX-S channel and hPN3 is a TTX-R channel blocked by TTX with an IC.sub.50=80 .mu.M. Rabbert also showed that sodium channels in mammalian DRG sensory neurons express at least two sodium currents: a TTX-sensitive current (TTX-SI.sub.Na) with rapid inactivation kinetics and a TTX-resistant current (TTX-RI.sub.Na) with slower inactivation kinetics. The biological role of the two sodium currents has not been delineated whereas numerous studies indicated that the properties of the TTX-RI.sub.Na currents in dorsal root ganglia appear well suited to contribute to the sustained neuronal firing characteristic of most neuropathic **pain** conditions.

SUMM Nociceptors are primary afferent neurons that respond to noxious or potentially tissue-damaging stimuli and are unique among sensory neurons because they can be sensitized. The decrease in the threshold and increase in the response to a constant stimulus that are characteristic of nociceptor sensitization are thought to underlie the hyperalgesia or tenderness associated with tissue injury. Agents released at the site of tissue injury sensitize nociceptors by initiating a cascade of event that likely results in a change in ionic conductance of the nociceptor peripheral terminal. Small-diameter sensory neurons in the DRG are known to express a TTX-R channel activity. A variety of inflammatory insults and direct damage to sensory neuron fibers produce a decrease in the thresholds of activation of sensory neurons, while prolonged activation of sensory neurons can lead to central sensitization to noxious input within the spinal cord. When sensory neurons were highly excited, activity of sodium channels and voltage-gated sodium current were increased significantly. Recent numerous studies suggest that increase of TTX-RI.sub.Na may play a significant role in the hyperexcitability of sensory neurons. Increased TTX-RI.sub.Na may contribute to diverse acute and chronic **pain** such as neuropathic **pain** and neuroma **pain** which were induced by inflammation and nerve damage. Patch-clamp electrophysiological techniques have been used to study the effects of hyperalgesic agents that modulate TTX-RI.sub.Na at primary culture DRG neurons. Evidence suggests that prostaglandin E.sub.2 (PGE.sub.2), adenosine and serotonin increase the magnitude of TTX-RI.sub.Na, shift its conductance-voltage relationship in a hyperpolarized direction, and increase its rate of activation and inactivation. In contrast, thromboxane B.sub.2, a cyclooxygenase product which does not produce hyperalgesia, does not affect TTX-RI.sub.Na.

These results suggest that an increase in TTX-RI.sub.Na underlies the increase in nociceptor neuronal sensitization induced by hyperalgesic agents. Intratheacal administration of antisense and sense oligodeoxynucleotides (ODN.sub.S), which were directed against a unique sequence of the rPN3 or SNS were used to examine the role of these channels in PGE.sub.2-induced hyperalgesia. Only antisense ODNs led to a decrease in PGE.sub.2-induced hyperalgesia. PGE.sub.2-induced hyperalgesia was partially recovered 4 days after the last antisense ODN injection, and was fully recovered within 7 days. Antisense ODNs selectively and significantly reduced TTX-RI.sub.Na current density in cultured sensory neurons. These finding support the hypothesis that modulation of TTX-RI.sub.Na contributes to inflammatory hyperalgesia.

SUMM Novakovis et al by their immunohistochemical studies, showed that sodium channels, especially PN3 channels, accumulated at the site of injury. The subcellular distribution of PN3 channels also changed after neuropathic injury, and nerve conduction was significantly altered. Sodium channel anterograde axonal transport is completely blocked in neuropathic **pain** and neuroma **pain** models, and is significantly reduced in the chronic constriction injury model of neuropathic **pain** (CCI). Because sodium channels, presumably including TTX-R channels, are constantly being transported to peripheral terminals, alterations in axonal transport ultimately result in channel accumulation at the injury site. Nerve degeneration and subsequent regeneration of many new axonal sprouts could be observed at the injury site in the CCI and neuroma models. Many of these new sprouts appear to be immunopositive for PN3. The overaccumulation of sodium channels occurs in regeneration fibers. Sensitization of CNS is an important characteristic of neuropathic **pain**. Establishment and maintainance of CNS sensitization relies on sense information conducted by nociceptor nerve fibers. In the **pain** state, because TTX-R channels are involved in coding information of **pain** sense, TTX-R channels are thought to play an important role in central perception of **pain** input.

SUMM In summary, modulation of TTX-R sodium channels is thought to play a role in the sensitization of nociceptors in the persistent **pain** state. The tissue distribution of TTX-R channels is restricted to a subpopulation of sensory neurons with properties of nociceptors. It is possible that designing a pharmacotherapeutic agent that selectively blocks TTX-R channels will be effective for **pain** relief. hPN3 may prove to be a valuable target for a therapeutic agent for treatment of acute and chronic **pain**.

SUMM TTX blocking of TTX-R channels may contribute to antinociceptive action of TTX in animals. In animal models of **pain**, neuromas, neuropathic **pain** or persistent dysesthesis initiated by artificial damage to peripheral sensory nerves produces ectopic discharges originating at both injury site and related dorsal root ganglia, and consequently hyperexcitability in associated dorsal horn (DH) neurons of spinal cord. TTX inhibits neuropathic ectopic activity in neuromas, DRG, and DH neurons in a dose-dependent pattern. However, at present the relative contribution of TTX-S and TTX-R channels to the generation of ectopic discharges in neuromas, DRG, and DH neurons is not clear.

SUMM TTX produces antinociceptive action at dose levels that do not significantly change behavior of animals. However, TTX at these dose levels does not modulate distribution and function of sodium channels, nor does TTX fully block nerve conduction in various types of **pain** conditions. These results suggest that TTX may unexpectedly act on TTX-R sodium channels to produce an antinociceptive action.

SUMM **Pain** may be acute or chronic. Acute **pain** can be

severe, but lasts a relatively short time. It is usually a signal that body tissue is being injured in some way, and the **pain** generally disappears when the injury heals. Chronic **pain** may range from mild to severe, and it is present to some degree for long periods of time. Chronic **pain** often arises without any detectable injury.

SUMM TTX is also effective for alleviating acute **pain** induced by mechanical and chemical stimulation, and inflammation.

SUMM Tetrodotoxin (TTX) has been shown to be effective on **pains** produced by liver cancer, rectal cancer, leiomyosarcoma, bone cancer, stomach cancer, lymphatic cancer, esophageal cancer and other major cancer types. TTX is also effective on central **pain**, chronic **pain** and phantom limb **pain**.

SUMM Tetrodotoxin is effective on all severe chronic **pains**. Tetrodotoxin is capable of generating analgesia in a mammal experiencing acute or chronic **pain**. The method of the present invention includes systemically (generally, to the whole body) administering, in a suitable pharmaceutical vehicle, an effective dose of a long-acting sodium channel blocking compound, i.e. tetrodotoxin.

SUMM **Pain** can originate for many reasons. A familiar cause is trauma, such as a sprain or muscle injury or broken bone, or from surgery. **Pain** due to inflammation, such as a toothache, is also familiar to many. Headache is a common experience and arises often for unknown reasons.

SUMM Cancer patients may have **pain** for a variety of reasons. It may be due to the effects of the cancer itself, or it could result from treatment methods. For example, after surgery a person feels **pain** as a result of the operation itself. Not all people with cancer have **pain**, and those who do are not in **pain** all the time.

SUMM Cancer **pain** may depend on the type of cancer, the stage (extent) of the disease, and the patient's **pain** threshold (tolerance for **pain**). Cancer **pain** that lasts a few days or longer may result from:

SUMM The difference between acute and chronic **pain** is discussed by Joseph T. Dipiro, "Pharmacotherapy: A Pathophysiologic Approach", Third Edition, Appleton & Lange (1997) p. 1263. Dipiro explains that acute **pain** may be a useful physiologic process warning individuals of disease states and potentially harmful situations. Unfortunately, severe, unremitting, undertreated **pain**, when it outlives its biologic usefulness, can produce many deleterious effects such as psychological problems. When **pain** is not effectively treated, the stress and concurrent reflex reactions often cause hypoxia, hypercapnia, hypertension, excessive cardiac activity, and permanent emotional difficulties. The problems associated with these reactions range from prolonged recovery time to death.

SUMM Under normal conditions, acute **pain** quickly subsides as the healing process decreases the **pain**-producing stimuli. However, in some instances **pain** may persist for months to years, leading to a chronic **pain** state with features quite different from those of acute **pain**. Typically, chronic **pain** is divided into four subtypes: **pain** that persists beyond the normal healing time for an acute injury, **pain** related to a chronic disease, **pain** without identifiable organic cause, and **pain** that involves both the chronic and acute **pain** associated with cancer. Patients in chronic **pain** often develop

severe psychological problems caused by fear and memory of past **pain**. In additional, chronic **pain** patients may develop dependence and tolerance to analgesics, have trouble sleeping, and more readily react to environmental changes that can intensify **pain** and the **pain** response. Distinguishing between chronic and acute **pain** states is very important because of differing management techniques.

SUMM Acute and chronic **pain** can also be classified by duration. Acute **pain** lasts or is anticipated to last less than 1 month, e.g., postoperative **pain**. Chronic **pain** is usually defined as **pain** persisting more than 1 month, e.g., cancer **pain** and phantom limb **pain**.

SUMM The National Institute of Neurological Disorders and Stroke, National Institutes of Health (http://healthlink/mcw.edu/article/921391401.html; Jun. 29, 2000) describes central **pain** syndrome as a neurological condition caused by damage specifically to the central nervous system (CNS)--brain, brainstem, or spinal cord. The **pain** is steady and is usually described as a burning, aching, or cutting sensation. Occasionally there may be brief, intolerable bursts of sharp **pain**.

SUMM Central **pain** is characterized by a mixture of **pain** sensations, the most prominent being constant burning. Mingled with the burning are sensations of cold, "pins and needles" tingling, and nerve proximity (like that of a dental probe on an exposed nerve). The steady burning sensation is increased significantly by any light touch. Patients are somewhat numb in the areas affected by this burning **pain**. The burning and loss of touch appreciation are usually most severe on the distant parts of the body, such as the feet or hands. **Pain** may be moderate to severe in intensity and is often exacerbated by movement and temperature changes, usually cold temperatures.

SUMM Central **pain** syndrome may develop months or even years after injury or damage to the CNS. The disorder occurs in patients who have, or have had, strokes, multiple sclerosis, limb amputations, or brain or spinal cord injuries.

SUMM Generally **pain** medications provide little or no relief for those affected by central **pain** syndrome. Patients should be sedated and the nervous system should be kept quiet and as free from stress as possible. Central **pain** syndrome is not a fatal disorder. But for the majority of patients, the syndrome causes intractable **pain**.

SUMM The best way to manage **pain** is to treat its cause. For example, whenever possible, the cause of **pain** from cancer is treated by removing the tumor or decreasing its size. To do this, the doctor may recommend surgery, radiation therapy, or chemotherapy. When none of these procedures can be done, or when the cause of the **pain** is not known, **pain**-relief methods are used.

SUMM In the past, analgesics were differentiated as peripheral (e.g., aspirin, acetaminophen) and central acting (opioids) analgesics. Due to current better understanding of **pain** relief and analgesics, it is now more accepted to distinguish between non-opioid and opioid analgesics.

SUMM Non-opioid analgesics are often effective for mild to moderate **pain** and in treating **pain** arising from rheumatoid arthritis. Typical non-opioid analgesics are aspirin, acetaminophen and other nonsteroid anti-inflammatory drugs (NSAIDs), e.g., ibuprofen,

piroxicam, and naproxen.

SUMM Opioid (or opiate) is a general term for natural or synthetic substances that bind to specific opioid receptors in the central nervous system producing an agonist action. Opioid analgesics are extremely useful in managing severe acute **pain**, postoperative **pain** and chronic **pain** including cancer **pain**. Typical opioid analgesics are codeine, morphine, methadone and fentanyl.

SUMM Traditional cancer **pain** relief methods include use of opiates such as codeine, hydromorphone (Dilaudid), levorphanol (Levo-Dromoran), methadone (Dolophine), morphine, oxycodone (in Percodan), and oxymorphone (Numorphan). They may be taken by mouth (orally, or PO), by injection (intramuscularly, or IM), through a vein (intravenously, or IV), or by rectal suppository. There are also other methods of giving **pain** medicines for more continuous **pain** relief. Not all narcotics are available in each of these forms.

SUMM NSAIDs similar to ibuprofen (in large doses, ibuprofen requires a prescription) are used for treatment of **pain** from cancer. Included in this group of **pain** relievers are Motrin, Naprosyn, Nalfon, and Trilisate. They are useful for moderate to severe **pain**. They may be especially helpful in treating the **pain** of bone metastasis.

SUMM The inventors have discovered that tetrodotoxin (TTX), its analogs and derivatives are effective on **pains** produced by cancers such as liver cancer, rectal cancer, leiomyosarcoma, bone cancer, stomach cancer, lymphatic cancer, esophageal cancer and other major cancer types. Tetrodotoxin and its analogs and derivatives are effective in relieving **pain** in humans and other mammals resulting from malignant neoplasm (cancers) or other tumors. These cancers can occur in the genital organs (including prostate), digestive system (including stomach, colon), breast, respiratory system (including lung and bronchus), urinary system, lymphoma and skin cancer.

SUMM A person who has had an arm or leg removed by surgery may still feel **pain** or other unpleasant sensations as if they were coming from the absent limb. Doctors are not sure why it occurs, but phantom limb **pain** is real; it is not imaginary. This also can occur if a patient had a breast removed, resulting in a sensation of **pain** in the missing breast.

SUMM No single **pain** relief method controls phantom limb **pain** in all patients all the time. Many methods have been used to treat this type of **pain**, including **pain** medicine, physical therapy, and nerve stimulation. Tetrodotoxin administered in accordance with the method of the invention provides relief from the **pain** associated with phantom limb **pain**.

SUMM Tetrodotoxin, its analogs and derivatives are effective in relieving **pain** in humans and other mammals resulting from malignant neoplasm (cancers) or other tumors. These cancers can occur in the genital organs (including prostate), digestive system (including stomach, colon), breast, respiratory system (including lung and bronchus), urinary system, lymphoma and skin cancer, as shown in the following examples.

SUMM Sodium channel blockers are surprisingly shown to be effective as long-term systemic analgesics for alleviation of severe **pain**. It is also surprising that minimal side effects, the principal one being numbness in the lips and extremities, are observed upon systemic administration. Patients debilitated by **pain** are able to resume almost normal lives for periods of more than 20 days following a

single course of treatment with TTX. That TTX and other sodium channel blockers can be used as systemic analgesics that are more effective than morphine and other opioid analgesics in treating acute, central and chronic **pain** is entirely unexpected.

SUMM An amount of a compound "effective for relieving **pain**" is an amount that results in a decrease in a patient's perception of **pain** by 2 units or more on the Numerical **Pain** Intensity Scale. An amount that is "very effective for relieving **pain**" is an amount that results in a decrease in a patient's perception of **pain** by 4 units or more on the Numerical **Pain** Intensity Scale. An amount of a compound "effective for eliminating **pain**" is an amount that results in a decrease in a patient's perception of **pain** to zero on the Numerical **Pain** Intensity Scale.

SUMM 1. Ran H P, Bevan S J, Dray A. Nociceptive peripheral neurones: cellular properties. In: Wall P D, Melzack R., editors. Textbook of **pain** , Edinburgh, chruchill livingstane, 1994; 57-78.

SUMM 2. Woolf C J, Doubell T P. The pathophysiology of chronic **pain** -increased sensitivity to low threshold A .beta.-fibre inputs. Current opinion in Neurobiology 1994; 4:525-534.

SUMM 3. Dray A. Tasting the inflammatory soup: the role of peripheral neurones. **Pain** Reviews. 1994; 1:153-173.

SUMM 4. Rabert D K, Koch B D, Ilnicka M, et al. A tetrodotoxin-resistant voltage-gated sodium channel from human dorsal root ganglia, hPH3/SCN 10A. **Pain** 1998; 78:107-114.

SUMM 8. Khasar S G, Gold M S, Levine J D, A tetrodotoxin-resistant sodium current mediates inflammatory **pain** in the rat, Neuroscience letters, 1998; 256:17-20.

SUMM 10. Omana-zapata I, Khabbaz M A, Hunter J C, et al. Tetrodotoxin inhibits neuropathil ectopic activity in neuromas, dorsal root ganglia and dorsal horn neurons, **Pain**, 1997; 72:41-49.

DETD A clinical study was carried out from Sep. 21 to Oct. 10, 1999 to examine the analgesic effect of tetrodotoxin injection (TTX purity 89%, brand name TETRODIN, batch no. 990122, Nanning Maple Leaf Pharmaceutical Co., Ltd., Guangxi, China) on 11 people who had chronic **pain** from advanced cancer.

DETD Eleven late term cancer patients volunteered to participate in this study. Computerized tomography (CT)-scans and pathological examination confirmed that all the patients had cancer. They all had moderate or severe **pain** according to the WHO endorsed criteria on " **pain** grading".

DETD Classification of **Pain** Intensity and Recording Method

DETD The protocol required that no other analgesic drugs be taken for 24 hours before participating in the study. Nor were any other analgesic drugs taken during the 3-day period of the use of tetrodotoxin. **Pain** was evaluated using the Numeric **Pain** Intensity Scale, which is described below. **Pain** was initially evaluated prior to the initial tetrodotoxin injection. After each administration of tetrodotoxin (at 8:00 AM and 8:00 PM each day), a research staff member observed and recorded the **pain** intensity of every patient at the following 14 time intervals: 5 min, 10 min, 15 min, 20 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h 7 h, 8 h, and 12 h.

DETD 2.1 Recording the Method of **Pain** Intensity

DETD For this test the WHO recommended method of 0.about.10 Numeric **Pain** Intensity Scale was used to calculate and record the **pain** intensity of the people in this test. Briefly, patients

would self-evaluate their **pain** based upon a 0 to 10 numeric scale as shown below and then report it to a research assistant. ##STR2##

DETD 0=no **pain**; 1-4=mild **pain**; 5-6=moderate **pain** ; 7-10=severe **pain**

DETD 3.1 **Pain** Intensity Difference (PID)

DETD PID is calculated by taking the **pain** intensity number before administration, and subtracting the **pain** intensity number at every time point after administration.

DETD 3.2 **Pain** Relief

DETD After calculating the patient's **pain** intensity at each time interval, the researcher assesses the **pain** relief and assigns a value from one of the following five choices.

DETD I: mild relief (the **pain** abates about 25%)

DETD II: moderate relief (the **pain** abates about 50%)

DETD III: significant relief (the **pain** abates about 75%)

DETD IV: complete relief (the **pain** disappears completely)

DETD **Pain** affects every patient's normal life and ability to continue with their everyday routine. This is generally referred to as their quality of life. Depending on the severity of the **pain** that is being experienced by each individual it can cause patients to experience irritability, depression and poor appetite. The researcher must consider any changes in the patient's quality of life, in the evaluation of the analgesic effect of any new drug. The numeric scale in the line below expresses the high and low reference numbers. It should be noted that this "quality of life" evaluation is a subjective issue and that the research doctor relies on the patient's descriptions of any changes (before and after administration of tetrodotoxin) in their quality of life as the primary means of input for making this evaluation. Issues that are questioned in regard to the quality of life include, routine daily activity, emotions, mobility (walking ability), normal work (includes both work outside the home and housework), sleeping state or pattern, relations with other persons, enjoyment of life.

DETD All subjects experienced various degrees of **pain** relief within 30 min. after the first administration of tetrodotoxin. Some of them reported noticeable **pain** relief in 5 min. After 3 days of the twice daily administration of tetrodotoxin, the **pain** intensity of all subjects was reduced to 0 in all but one patient who recorded a 1.

DETD The results demonstrate that all of the patients, were totally relieved of their **pain** for between 20-30 days after the final administration of tetrodotoxin on the 3rd day. None of the patient's showed the slightest signs of having any symptoms of addiction following the three days of tetrodotoxin administration.

DETD The patients reported that their "quality of life" was affected negatively, either moderately or severely by the **pain** caused by their cancer and/or their cancer treatment and medication. During the three day tetrodotoxin treatment and for the following 20.about.30 days, their quality of life showed distinct and dramatic improvements that were described, for example as severe interference that was reduced to moderate or mild interference. After 3 days of administration of tetrodotoxin, most of the patients could return to a normal life. Some of them returned to playing the popular game mahjong (a type of Chinese playing cards) with healthy people. They were able to go to the public bathhouse to bathe, an activity that had become to difficult to do due to the **pain** and anguish caused by the cancer. One of them took a long journey from Harbin to Beijing by train.

DETD 5.1 Less frequent administration of tetrodotoxin is required. The patient only needs one injection of 30 .mu.g every 12 hours for up to 3 days. With these patients, the three-day administration of tetrodotoxin was immediately effective in reducing or eliminating their **pain** .

DETD 5.4 Analgesic effect lasts longer. After 3 days of the twice daily

administration of tetrodotoxin, the analgesic effect lasted 20-30 days. No patient reported the reappearance of **pain** in the period from the fourth to the twentieth day. In most instances the **pain** relief was effective for the entire 30 day monitoring period.

DETD 5.8 Tetrodotoxin improves the condition of cancer patients during their treatment. Tetrodotoxin does not have any direct effect on any of the cancers themselves. However, it was observed that the overall health and mental attitude of the patients improved substantially as they were relieved of the **pain** from their cancer.

DETD Mr. Gao, is a 44 year old male. He developed abdominal **pain** and was diagnosed with smooth muscle **pain** in the back wall of his celiac for which he underwent a surgical procedure. One year later, his abdomen **pain** relapsed and he was operated on again. The pathological examination from the second operation revealed that he had developed a smooth muscle sarcoma (leiomyosarcoma), later finding that his sarcoma had spread to his liver and that he now required and received anti-cancer treatment (chemotherapy). He began to inject Dolantin, because he could not bear the severe **pain** in his abdomen. He needed to inject Dolantin at least 3 times per day. Initially he was taking the Dolantin by intramuscular injection, and finally he needed to use intravenous injection in order to have the Dolantin take effect faster. Just prior to when he received the **tetrodotoxin** treatment, he had taken over 100 injections of Dolantin in the previous month. At the beginning, when he stopped using Dolantin, he experienced **morphine**-like withdrawal symptoms, such as whole body weakness and **pain**, trembling when standing up and difficulty walking. He voluntarily received **tetrodotoxin** treatment. His **pain** intensity scale was 8 before using **tetrodotoxin**. 5 minutes after the first injection of **tetrodotoxin**, his **pain** intensity on the 0 to 10 scale decreased to 0. After 3 days of treatment, he was able to go to the public bathhouse to bathe by himself. He went to a friend's home to play mahjong. To the date of this report, he is living normally and continues to feel comfortable without any **pain**.

DETD Mr. Zhang, is a 26 year old male. He felt **pain** in his liver area and was diagnosed with advanced liver cancer. His illness progressed to where he could not bear the severe abdominal **pain** and abdominal distention. He began to use Dolantin and other painkillers to relieve his **pain**. He volunteered to receive tetrodotoxin treatment. Before the first administration of tetrodotoxin, his **pain** intensity on the 0 to 10 scale was 8. On the second day of injecting tetrodotoxin, his **pain** intensity was reduced to 0. His life quality was also improved significantly. After completing 3-day's treatment, he traveled by train from Harbin to Beijing for further treatment of his cancer.

DETD Ms. Xie is a 76 year old female. She was diagnosed with rectal cancer and underwent surgery in 1996. In 1998, her rectal cancer spread to her liver. Her **pain** increased to where she was having difficulty dealing with the **pain**. She voluntarily received tetrodotoxin treatment. Her **pain**, intensity scale was reduced to 0 from 6, within 20 minutes after the first injection of tetrodotoxin. Her quality of life score also decreased to 6 from 10 after the first injection of tetrodotoxin. At the end of the 3 days of treatment with tetrodotoxin, she recovered to what she considered to be her normal life-style.

DETD Mr. Jin is a 63 year old male. He suffered from liver cancer for 8 years. In the last 6 months, his **pain** had escalated to where he could not be relieved of his **pain** by the use of other painkillers. He volunteered to receive the tetrodotoxin treatment. His **pain** intensity scale decreased to 0 from 7 on the second day of the tetrodotoxin treatment. His quality of life was also improved significantly.

DETD Ms. Duang, a 46 years old female, was diagnosed with lumbago, after which the symptoms associated with the lumbago gradually worsened. Painkillers were effective for managing the **pain** from her

lumbago. Six months prior to this test, she started to experience **pain** in her left leg that became more and more severe. She was prescribed the progressively stronger painkillers, Tramadol, Pentazocine and Dolantin during this six months. During this same six months she was diagnosed with cancer that was initially of the liver, and had metastasized to bone cancer. The bone cancer was located in the L.sub.3, L.sub.4 and T.sub.11 vertebrae and was evidenced by the presence of osteolytic lesions. Ms Duang volunteered to receive tetrodotoxin treatment. Immediately prior to starting the tetrodotoxin treatment, her **pain** intensity on the 0 to 10 scale was 9. Ten minutes after her first injection of tetrodotoxin, her **pain** intensity decreased to 7, and 20 minutes after her first injection, her **pain** intensity decreased to 2. At the conclusion of the 3 days treatment with tetrodotoxin her **pain** was entirely eliminated.

DETD Ms. Li is a 72 year old female who was experiencing abdominal distension and poor appetite. When an initial treatment did not take effect, an ultrasonic examination of her abdomen was done and she was diagnosed to have cancer of the liver. Her cancer appeared to be relieved after treatment by chemotherapy, but her abdominal distension and abdominal **pain** became worse. By the start of the test use of tetrodotoxin the painkillers that she was using could not relieve her **pain**. She volunteered to receive tetrodotoxin treatment in an attempt to reduce her **pain**. Before the administration of tetrodotoxin, her **pain** intensity on the 0 to 10 scale was 7. Ten minutes after she received her first of tetrodotoxin, her **pain** intensity scale was reduced to 0. After 3 days of treatment with tetrodotoxin, she was able to carry on with her life as if she had recovered back to normal.

DETD Mr. Li is a 36 year old male, who was diagnosed with advanced liver cancer. The **pain** in the region of his liver had increased to where he was not relieved of his **pain** by intramuscular injections of Dolantin. He volunteered to receive tetrodotoxin treatment. Previous to the administration of tetrodotoxin, his **pain** intensity on the 0 to 10 scale was 7. Twenty minutes after the first injection of tetrodotoxin, his **pain** intensity was reduced to 3. After the third injection of tetrodotoxin his **pain** intensity stabilized at 0. After 3 days of treatment his quality of life had improved significantly, achieving.0 interference.

DETD Mr. Cheng is a 60 year old male. He was diagnosed with mucinous adreno-carcinoma of the stomach and received surgery to remove the cancer. Three months after the operation, his abdomen became distended and he started to experience severe abdominal **pain**. A CTscan showed that the cancer had further extensively spread to his lungs, liver, abdominal cavity and lymph nodes. He volunteered to receive tetrodotoxin treatment. Prior to the first administration of tetrodotoxin, his **pain** intensity on the 0 to 10 scale was 8. Twenty min after injecting tetrodotoxin his **pain** intensity scale reduced to 0. After 3 days treatment he recovered to what he considered a normal life.

DETD Mr. Shi is a 59 year old male. He was diagnosed with carcinoma of the esophagus after one year of consistent retro-sterna **pain** that eventually became dysphagia. This was so severe in the last month that it was causing him to vomit after eating. After having surgery to remove the cancer, his **pain** was severe and was not relieved from the regular injections of Dolantin that he was prescribed. He volunteered to receive tetrodotoxin treatment. Prior to his first administration of tetrodotoxin, his **pain** intensity on the 0 to 10 scale was 8. After the second injection of tetrodotoxin, his **pain** intensity was reduced to 0. Following the 3 days of tetrodotoxin treatment he had recovered to what he considered a normal life.

DETD Ms. Liu is a 69 year old female who, three years after her operation to remove stomach cancer, found that the lymph node of her left cervical was swelling. A pathological examination showed that her stomach cancer had spread to the lymph node. For some time before she volunteered to

receive tetrodotoxin treatment, her **pain** had increased to where she had difficulty dealing with it. Before the first administration of tetrodotoxin, her **pain** intensity on the 0 to 10 scale was 9. Three hours after the first injection of tetrodotoxin, her **pain** intensity scale reduced to 2, and after 3 days of treatment with tetrodotoxin, her **pain** intensity scale stabilized at 0.

DETD Ms. Tan is a 52 year old female whose rectal cancer relapsed one year after she had undergone surgery. The lump in her perineum was abscessed. The regional **pain** was extreme and was accompanied by headaches and dizziness at times so severe that she could not speak. She volunteered to receive tetrodotoxin treatment. Before the first administration of tetrodotoxin her **pain** intensity on the 0 to 10 scale was 7. One hour after the first injection of tetrodotoxin, her **pain** intensity was reduced to 0. At the completion of 3 days of treatment with tetrodotoxin she recovered to what she considered a normal life.

DETD

TABLE 3

Summary of Tetrodotoxin Treating Cancer **Pain**

No.	Name	Sex	Age	Disease Progress	Type of **Pain**	Dosage (.mu.g)	**Pain** Rate Before treatment	**Pain** Rate after Treatment	Side Effect(s)
1	Gao HM	M	44	Smooth muscle sarcoma, spread to liver	Local **pain**, whole body **pain**	180	8	0	Numbness, nausea, vomit
2	Zhang BL	M	26	Late liver cancer	Colicky **pain**, swelling **pain**	180	6	0	Numbness
3	Xie SHQ	F	76	Rectal cancer, spread to liver	Dull **pain**, Local **pain**, whole body **pain**	180	6	0	Numbness
4	Jin DX	M	63	Liver cancer	Local **pain**, dull **pain**	180	7	0	Numbness
5	Duan YQ	F	46	Liver cancer, spread to bone	Stabbing **pain**	180	9	1	Numbness
6	Li SHQ	F	72	Liver cancer	Colicky **pain**, swelling **pain**	180	7	0	Numbness
7	Li BF	M	36	Late liver cancer	Colicky **pain**, swelling **pain**	180	7	0	Numbness
8	Cheng B	M	60	Stomach cancer	Local **pain**, dull **pain**	180	8	0	Numbness, nausea, vomit
9	Shi CHF	M	59	Postoperative relapse of carcinoma of esophagus	Local **pain**, dull **pain**	180	8	0	Numbness
10	Liu SM	F	69	Stomach cancer, lymphatic metastasis	Local **pain**, dull **pain**	180	9	0	Numbness
11	Tan XCH	F	52	Postoperative relapse of rectal cancer	Local **pain**, dull **pain**	180	7	0	Numbness

DETD Wistar rats were randomly divided into a TTX-tested group, positive control group (Morphine) and a negative control group (normal saline). The rats were fasted for 12 hours before the test, meanwhile allowed to drink water ad-libitum. 2.5% Formalin was used as the **pain** stimulus. TTX was injected i.m. or s.c. in the rats at different doses

and then they were held in 20 cm.times.20 cm.times.20 cm clear plastic boxes for observation. Forty minutes later, 0.06 ml 2.5% Formalin was injected s.c. in the plantar surface of the right hind paw of rats. The **pain** responses of the rats, such as licking/gnawing, twitching, and lifting the right hind paw, were observed and recorded in the following 5 minutes. **Pain** response scores were calculated using the following formula:

DETD **Pain** response score=licking/gnawing time (sec).times.3+twitching occurrences.times.2/3+lifting time (sec).

DETD The rats in the normal saline (NS) group and morphine group were treated similarly. The inhibition rate of TTX on **pain** responses was calculated by:

DETD Inhibition rate (%)=(the average of the **pain** response scores of the control group-that of the TTX group)/the average of the **pain** response scores of the control group.times.100%.

DETD

TABLE 6

The ID.sub.50 values (sc) of TTX and Morphine in Formalin test in rats

Group	Number of animals	Scores of **pain** responses	Inhibition rate (%)	ID.sub.50 (95% CI)
NS control	8	237.5		
TTX (.mu.g/kg)				
0.3	8	186.4	21.5	0.82 (0.66 .about. 1.00)
0.6	8	132.9	44	.mu.g/kg
1.25	8	72.1	69.6	
2.5	8	67.3	71.7	
5.0	8	41.3	82.6	
Morphine (mg/kg)				
0.6	8	210.7	11.3	2.63 (2.32 .about. 2.98)
1.25	8	190.7	19.7	mg/kg
2.5	8	158.2	33.4	
5.0	8	46.1	80.6	
10.0	8	13.1	94.2	

DETD

TABLE 7

The ID.sub.50 values (im) of TTX and Morphine in Formalin test in rats

Groups	Number animals	Scores of **pain** responses	Inhibition rate (%)	ID.sub.50 (95% CI)
NS	20	203.6		
TTX (.mu.g/kg)				
0.25	10	152.7	25.0	0.93
0.50	10	116.0	43.0	(0.56 .about. 1.56)
2.50	10	57.2	71.9	.mu.g/kg
5.0	10	48.5	76.2	
10.0	10	45.9	77.5	
Morphine (mg/kg)				
2.5	10	131.2	35.6	
3.5	10	51.6	74.6	2.74
5.0	10	30.1	85.2	(2.24 .about. 3.35)
6.5	10	22.7	88.9	mg/kg
8.0	10	5.2	91.0	

DETD The analgesic effects of TTX and morphine on thermal-induced

pain were studied by the tail-flick test in rats.

DETD Rats were randomly divided into 7 groups, each consisting of 8 rats. The rats were fasted for 12 hours before testing, but allowed to drink water ad-libitum. A rat was immobilized on a tail-flick algometer, and then a loading electric voltage of 12 V was applied to a light bulb as a thermal stimulus to the tail end of the rat, and the tail-flick latency was recorded subsequently. If a rat did not respond within a period of 5-8 seconds, it would be rejected. The testing was performed after TTX was injected. If the **pain** threshold rose so high, such that the rat failed to flick its tail within 20 seconds of exposure to the stimulation, the illumination would be terminated to avoid blistering and damage to the skin. In such a case, the latency was considered to be 20 seconds.

DETD The results showed that TTX, at dose levels of 1.25.about.5.0 .mu.g/kg, produced pronounced analgesia effects on thermal induced **pain** in the tail-flick test in rats, but did not at lower dose levels of 0.3.about.0.6 .mu.g/kg. These effects were less potent than morphine (see Table 8).

DETD

TABLE 8

Analgesia effects of TTX and morphine on thermal-induced **pains** in the tail-flick test in rats

Group	Number of animals	Latency time (minutes)
Normal saline control	8	7.6 .+-. 3.8
TTX (.mu.g/kg)		
0.3	8	8.3 .+-. 3.7*
0.6	8	10.3 .+-. 4.9*
1.25	8	13.9 .+-. 4.2**
2.5	8	17.0 .+-. 3.5***
5.0	8	17.3 .+-. 3.8***
Morphine (mg/kg)		
5.0	8	>20

{overscore (X)} .+-. SD

*P > 0.05

**P < 0.05

***P < 0.01, compared to the normal saline control group.

CLM What is claimed is:

1. A method for producing analgesia in a mammal experiencing **pain** comprising systemically administering an amount of a composition comprising a sodium channel blocking compound, in a suitable pharmaceutical vehicle, effective to alleviate the **pain**.

4. The method of claim 1, wherein the **pain** is caused by mechanical, chemical or ischemic stimulation, or inflammation.

5. The method of claim 1, wherein the **pain** is neuropathic **pain**.

6. The method of claim 1, wherein the **pain** arises from cancer.

21. The method according to claim 6, wherein the **pain** arises from a cancer selected from the group consisting of liver cancer, rectal cancer, leiomyosarcoma, bone cancer, stomach cancer, lymphatic cancer, esophageal cancer, cancers in the genital organs, prostate cancer, digestive system cancer, stomach cancer, colon cancer, breast cancer, respiratory system cancer, lung cancer, bronchial cancer, urinary system cancer, lymphoma and skin cancer.

ACCESSION NUMBER: 2002:144258 USPATFULL
TITLE: Method of analgesia
INVENTOR(S): Dong, Qingbin, Nanning City, CHINA
Shum, Frank Hay Kong, North Point, HONG KONG
PATENT ASSIGNEE(S): Wex Medical Instrumentation Co., Ltd., North Point, HONG KONG (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6407088	B1	20020618	
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PRIORITY INFORMATION:	CN 2000-124517	20000918

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LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch LLP
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 2110
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L85 ANSWER 10 OF 10 USPATFULL on STN

AB This invention relates to the use of amino hydrogenated quinazoline compounds and derivatives thereof, such as **tetrodotoxin**, for abstaining from drug dependence in human. Such compounds are administered by subcutaneous, intramuscular or intravenous injection for abstaining from drug dependence, the said drug is alkaloids and nitrogen-containing non-amino acid compound, for example opium, **morphine**, heroin and the like. Such compounds without drug dependence and low toxicity and side effect can abstain rapidly from drug dependence.

SUMM (1). TTX produces pronounced analgesic effect on various **pains** caused by burning, trauma, injuries from falls, fractures, contusions and strains, especially for neuragia, myalgia and arthralgia. Unless the diseases are inveterate, TTX is a powerful analgesic.

SUMM (3). As a potent analgesic for late cancer patients. TTX exerted satisfactory effect of **pain** relieving on cancer **pain**, and no drug addiction cases were reported [Kao C Y, Pharm. Rev. 18(2):997, 1966]

SUMM (1) TTX was reportedly effective on **pain** relieving for lepers (Nomiyama S: Fed. Proc.31:1 117,1972)

SUMM The above-mentioned amino hydrogenated quinazoline compounds and derivatives thereof, including **Tetrodotoxin**, could inhibit the **morphine**'s-dependence withdrawal symptoms, and it is not addicted by the antagonists. It could effectively and promptly inhibit and allay the withdrawal symptoms and could dispel the restlessness of patients as use of these kinds of compounds with adequate dosage when the withdrawal response commences upto the most severe. The withdrawal symptoms of patients were allayed and disappeared from 5 to 30 min after accepted administration of the therapy. Patients could be quiet and almost feel numb in month, tongue and lips, however, no uneasy feeling. The numb counteracts the desire of patients for drugs, such as heroin. After several days maintenance (2-8 days, and generally 2-3 days), it reaches the clinical de-addiction which shows as the withdrawal symptoms disappeared completely and the test of **morphine** in urine transforms to negative. After halt in using the above-mentioned amino

hydrogenated quinazoline compounds and derivatives thereof, there is no dependence to them and no adverse and side effects. As using the above-mentioned amino hydrogenated quinazoline compounds and derivatives thereof to treat patients, no case developed sicchasia, vomiting, collapse or coma as with the use of other medicines. It also has no side effects as in the treatment of **methadone** and DHE.

DETD Almost every serious cases felt systematic **pain**, tiredness at the later phase of the de-abstinence treatment.

DETD TABLE 4

Evaluating Marks on Withdrawal Syndrom before and after Treatment

Withdrawal syndrome	Group A before (15 min) after 72 hrs	Group B before (15 min) after 72 hrs	Group C1 before (15 min) after 72 hrs	Group C2 before (15 min) after 72 hrs	Group D1 before (15 min) after 72 hrs	Group D2 before (15 min) after 72 hrs
Lacrimation	983(81)1	985(180)120	246(210)171	245(208)71	19(20)17	18(3)19
Salivation	980(40)31	1000(112)101	250(167)198	250(200)77	20(20)18	19(3)20
Yawns	921(450)21	999(720)57	250(172)98	250(198)42	20(20)16	20(10)20
Insomnia	998(350)98	998(620)512	250(160)198	25(220)72		

19(19)17
19(18)18
Gooseflesh
921(80)2
958(120)81
245(42)25
246(41)41
17(19)18
18(18)18
Vomiting
142(0)0
167(34)11
47(40)3
50(41)0
7(8)8
4(1)8
Nausea
640(0)0
941(100)20
236(41)7
225(40)3
I5(17)15
14(7)11
Anorexia
945(400)41
958(801)122
241(202)51
240(240)230
18(19)20
19(17)19
Anxiet and
998(151)123
998(670)210
250(240)50
250(210)17
19(20)19
18(17)20
restlessness
Systemic
888(101)140
966(121)720
248(240)247
241(240)247
17(19)18
17(13)18
Pain
Abdominal-
850(32)21
900(401)126
247(128)33
235(131)17
I5(16)14
16(16)17
gia &
diarrhea
Muscular
683(121)90
590(252)257
130(60)57
150(48)12
11(11)13
10(13)17
tremors
Rapid pulse

830(71)3
835(307)123
213(200)35
215(147)35
10(14)18
10(14)19

Cold & hot
958(21)0
960(25)3
249(120)7
245(98)8
18(20)19
17(14)18

Pupil (mm)
2.8 .+-. 0.3
2.9 .+-. 0.8
2.3 .+-. 0.5
2.8 .+-. 0.5
2.5 .+-. 0.4
2.4 .+-. 0.7
1.4 .+-. 0.8
1.8 .+-. 0.5
1.3 .+-. 0.7
1.9 .+-. 1.0
1.9 .+-. 1.1
1.7 .+-. 0.7

Weakness
767(667)672
880(701)8.08
245(245)246
225(224)248
15(17)19
18(7)19

Thirsting for
999(450)720
1000(661)881
250(249)125
250(230)247
20(20)20
20(19)20

DSM-III-R Diagnostic Criterion
DETD

TABLE 7

Withdrawal Syndrome of the Patients before Using the Compound of the Present Invention

Case No. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Subjective symptom
Agitating + + + + + + + + + + + + + + + + + +
Joint **pain** + + + + + + + + + + +
Cold + + + + + + + + + + + + + + + + + + +
Insomnia + + + + + + + + + + + + + + + + + + +
Exciting + + + +
Thirsty + + + + + + + + +
Dyspnea
Headache + + + + + + +
Abdominal **pain**

```
         +   +   + + + +     + +   +   + +      +
                                           +
Nausea     + + +   + + +     + +   +   + +      +
                                           +
Lower    +     + +   + +   +   + +     + + +
extremity sore
Thoracic   +     +     +   +     + +            +
depress
Stomachache
         +   +   +   +                          +
Objective symptom
Yamns    + + + + + + + + + + + + + + + + + +    +
                                           +
Skin itch
         + +   +       +       + +     + +      +
                                           +
Lacrimation
         + + + + + + + + + + + + + + + + + +    +
                                           +
Finger-tremors
           +     + +   + + +       +     +
Rhinorrhea
         + + + + + + + + + + + + + + + + + +    +
                                           +
Mydriasis
         +   +             +           +        +
Miosis     +
Vomiting   + + +   +   +             + + +      +
                                           +
Dysentery
         +       +   +       +
Nausea     +   +   + +     + +     +       +    +
Salivation
         + + + + + + + + + + + + + + + + + +    +
                                           +
Toss about
         + +         +             +   +        +
Feet agitating + +
Borborygmi
         + +             +         +   +   +
Cough      + + + + +                   +
Disturbance  +       +   +         +
Groan    + +         +       +     +
Diaphoresis
         +
Proteinuria
         + +   + + +       + +       +     +    +
                                           +
Respirating
         2 2 1 2 2 2 2 2 2 2 1 2 2 2 2 2 2 2    2
                                           2
number/min
         0 0 8 0 0 0 0 0 0 0 8 0 0 0 0 0 0 0    0
                                           0
Pulse    8 8 8 8 8 9 9 8 8 8 8 7 8 8 7 9 9 8    8
                                           8
         8 4 0 8 2 0 0 4 8 4 0 2 4 2 6 0 0 4    4
                                           8
Blood pressure
         9 1 1 9 9 9 9 1 9 9 1 1 1 9 9 1 9 9    9
                                           9
         0/
           0 0 0/
                 0/
```

```
              0/
                0/
                  0 6/
                      0/
                        0 0 0 0/
                                6/
                                  0 0/
                                      0/   0/
                                      0
    6 0/
        0/
          8 6 6 6 0/
                    7 6 0/
                          0/
                            0/
                              6 6 0/
                                    6 6    8
                                      /
    0 7 7 0 0 0 0 7 0 0 7 8 7 0 8 7 0 0    0
                                      7
      0 0         0     0 8 0     0        0
```

ACCESSION NUMBER: 1998:154282 USPATFULL

TITLE: Use of amino hydrogenated quinazoline compounds and derivatives thereof for abstaining from drug dependence

INVENTOR(S): Pan, Xinfu, Beijing, China
Qiu, Fanglong, Hunan, China

PATENT ASSIGNEE(S): Nanning Maple Leaf Pharmaceutical Co., Ltd., Guangxi Province, China (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5846975		19981208	
	WO 9524903		19950921	
APPLICATION INFO.:	US 1996-640781		19960521	(8)
	WO 1995-CN16		19950311	
			19960521	PCT 371 date
			19960521	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	CN 1994-110873	19940317

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: MacMillan, Keith D.
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 1004
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s e25
L6           1 107-21-1/BI

=> d

L6   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   107-21-1  REGISTRY
CN   1,2-Ethanediol (9CI)   (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Ethylene glycol (8CI)
CN   Glycol (6CI, 7CI)
OTHER NAMES:
CN   1,2-Dihydroxyethane
CN   1,2-Ethylene glycol
CN   146AR
CN   2-Hydroxyethanol
CN   Dowtherm SR 1
CN   Ethylene alcohol
CN   Ethylene dihydrate
CN   Fridex
CN   Glycol alcohol
CN   Macrogol 400 BPC
CN   MEG 100
CN   Monoethylene glycol
CN   Norkool
CN   NSC 93876
CN   Ramp
CN   Tescol
CN   Ucar 17
CN   Union Carbide XL 54 Type I De-icing Fluid
CN   Zerex
FS   3D CONCORD
DR   37221-95-7, 71767-64-1
MF   C2 H6 O2
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB,
       CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB,
       DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2,
       ENCOMPPAT, ENCOMPPAT2, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA,
       MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*,
       SPECINFO, SYNTHLINE, TOXCENTER, TULSA, ULIDAT, USPAT2, USPATFULL, VETU,
       VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)
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$HO-CH_2-CH_2-OH$

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

          38710 REFERENCES IN FILE CA (1947 TO DATE)
           3510 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
          38775 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s e26
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L7          1 112-80-1/BI

=> d

L7   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   112-80-1  REGISTRY
CN   9-Octadecenoic acid (9Z)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   9-Octadecenoic acid (Z)-
CN   Oleic acid (8CI)
OTHER NAMES:
CN   .DELTA.9-cis-Octadecenoic acid
CN   .DELTA.9-cis-Oleic acid
CN   9-cis-Octadecenoic acid
CN   9-Octadecenoic acid, (Z)-
CN   9Z-Octadecenoic acid
CN   cis-.DELTA.9-Octadecenoic acid
CN   cis-9-Octadecenoic acid
CN   cis-Oleic acid
CN   D 100
CN   D 100 (fatty acid)
CN   Edenor ATi05
CN   Edenor FTi05
CN   Emersol 205
CN   Emersol 211
CN   Emersol 213NF
CN   Emersol 214NF
CN   Emersol 233
CN   Emersol 6313NF
CN   Extra Oleic 80R
CN   Extra Oleic 90
CN   Extra Oleic 99
CN   Extra Olein 80
CN   Extra Olein 90R
CN   Extraolein 90
CN   Industrene 105
CN   Lunac O-CA
CN   Lunac O-LL
CN   Lunac O-P
CN   Lunac OA
CN   NAA 35
CN   Neo-Fat 92-04
CN   Oleine 7503
CN   Pamolyn 100
CN   Priolene 6906
CN   Priolene 6907
CN   Priolene 6928
CN   Priolene 6930
CN   Priolene 6933
CN   Vopcolene 27
CN   Wecoline OO
CN   Z-9-Octadecenoic acid
FS   STEREOSEARCH
DR   8046-01-3, 56833-51-3, 17156-84-2
MF   C18 H34 O2
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB,
       CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB,
       DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2,
       ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB,
       IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PIRA,
       PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, USAN, USPATFULL, USPAT2,
       VETU, VTB
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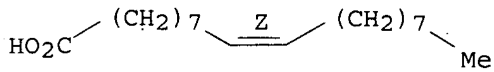
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Double bond geometry as shown.



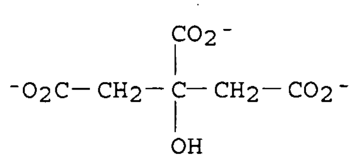
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

39642 REFERENCES IN FILE CA (1947 TO DATE)
2190 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
39714 REFERENCES IN FILE CAPLUS (1947 TO DATE)
11 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s e27
L8 1 126-44-3/BI

=> d

L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN **126-44-3** REGISTRY
CN 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, ion(3-) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Citric acid, ion(3-) (8CI)
OTHER NAMES:
CN Citrate
CN Citrate ion
CN Citrate ion(3-)
CN Citrate trianion
CN Citrate(3-)
FS 3D CONCORD
DR 20230-95-9, 20230-96-0, 142469-10-1, 147100-21-8
MF C6 H5 O7
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CHEMCATS, CIN, CSNB, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, NIOSHTIC, PIRA, PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL
(*File contains numerically searchable property data)



1023 REFERENCES IN FILE CA (1947 TO DATE)
26 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1024 REFERENCES IN FILE CAPLUS (1947 TO DATE)

=> s e28
L9 1 13072-89-4/BI

=> d

```
L9   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   13072-89-4  REGISTRY
CN   6,10-Epoxy-4,8,11a-metheno-11aH-oxocino[4,3-f][1,3,5]oxadiazepine-6,9,11-
     triol, 2-amino-1,4,5a,6,8,9,10,11-octahydro-9-(hydroxymethyl)-,
     (4S,5aS,6S,8R,9S,10S,11S,11aR,12R)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Tetrodotoxin, 4,9-anhydro- (8CI)
CN   Tetrodotoxin, 4,9-dideoxy-4,9-epoxy-, (4.beta.,9.beta.)-
CN   Tetrodotoxin, anhydro- (7CI)
OTHER NAMES:
CN   4,9-Anhydrotetrodotoxin
CN   Anhydroepitetrodotoxin
CN   Anhydrotetrodotoxin
FS   STEREOSEARCH
DR   7724-36-9, 16998-61-1, 17289-89-3, 2054-43-5
MF   C11 H15 N3 O7
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS,
       CASREACT, MEDLINE, NAPRALERT, RTECS*, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
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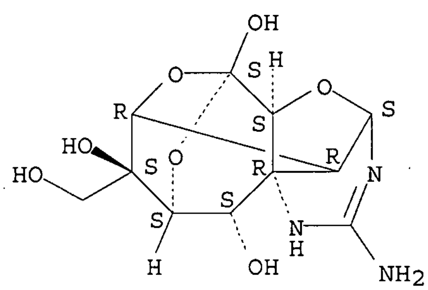
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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             89 REFERENCES IN FILE CA (1947 TO DATE)
             89 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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E17          1     KANG YUHUI/AU
E18          1     KANG YUJAN/AU
E19          1     KANG YUJING/AU
E20          1     KANG YUJUN/AU
E21          1     KANG YUL/AU
E22          1     KANG YULI/AU
E23          2     KANG YULIN/AU
E24          1     KANG YULING/AU
E25          1     107-21-1/BI
E26          1     112-80-1/BI
E27          1     126-44-3/BI
E28          1     13072-89-4/BI
E29          1     14213-97-9/BI
E30          1     14265-44-2/BI
E31          1     3270-35-7/BI
E32          1     35523-89-8/BI
E33          1     4368-28-9/BI
E34          1     55-68-5/BI
E35          1     56-81-5/BI
E36          1     57-15-8/BI
E37          1     57-55-6/BI
E38          1     62-38-4/BI
E39          1     64-19-7/BI
E40          1     69-65-8/BI
E41          1     7647-01-0/BI
E42          1     7647-14-5/BI
E43          1     77-92-9/BI
E44          1     7724-38-1/BI
E45          1     7724-39-2/BI
E46          1     7724-40-5/BI
E47          1     7724-41-6/BI

=> s e29
L10          1 14213-97-9/BI

=> d

L10  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   14213-97-9  REGISTRY
CN   Borate (BO33-) (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Borate
CN   Borate ion (BO3-3)
CN   Borate ion(3-)
CN   Boric acid (H3BO3), ion(3-)
CN   Boric acid ion(3-)
CN   Boron trioxide(3-)
CN   Orthoborate
MF   B O3
CI   COM
LC   STN Files:   BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CIN, EMBASE,
       GMELIN*, IFICDB, IFIPAT, IFIUDB, PIRA, PROMT, TOXCENTER, TULSA, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)
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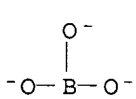

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          432 REFERENCES IN FILE CA (1947 TO DATE)
           20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
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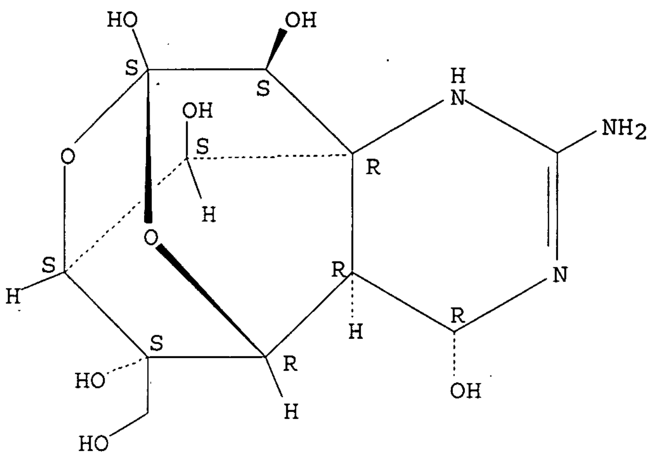
Other Sources: EINECS**
    (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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            2237 REFERENCES IN FILE CA (1947 TO DATE)
              33 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            2241 REFERENCES IN FILE CAPLUS (1947 TO DATE)
               9 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e34
L15          1 55-68-5/BI

=> d

L15   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN    55-68-5  REGISTRY
CN    Mercury, (nitrato-.kappa.O)phenyl- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN    Mercury, (nitrato-O)phenyl-
CN    Mercury, nitratophenyl- (8CI)
CN    Phenylmercury nitrate (6CI)
OTHER NAMES:
CN    Merphenyl nitrate
CN    Mersolite 7
CN    Nitratophenylmercury
CN    NSC 4772
CN    Phe-Mer-Nite
CN    Phenalco
CN    Phenitol
CN    Phenmerzyl nitrate
CN    Phenylmercuric nitrate
CN    Phenylmercurinitrate
CN    Phenylmercury (II) nitrate
MF    C6 H5 Hg N O3
CI    COM
LC    STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
        BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS,
        CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB,
        IFIPAT, IFIUDB, IPA, MRCK*, MSDS-OHS, NIOSHTIC, PROMT, RTECS*,
        TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
          (*File contains numerically searchable property data)
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    Other Sources:   EINECS**, NDSL**, TSCA**
        (**Enter CHEMLIST File for up-to-date regulatory information)



Ph— Hg— O— NO2

             308 REFERENCES IN FILE CA (1947 TO DATE)
               4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             308 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              47 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e35
L16           1 56-81-5/BI

=> d

L16  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   56-81-5  REGISTRY
CN   1,2,3-Propanetriol (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Glycerol (8CI)
CN   Propanetriol (7CI)
OTHER NAMES:
CN   1,2,3-Trihydroxypropane
CN   42: PN: US20030109453 SEQID: 41 claimed sequence
CN   Bulbold
CN   Cristal
CN   E 422
CN   Glyceol Opthalgan
CN   Glycerin
CN   Glycerine
CN   Glyceritol
CN   Glycyl alcohol
CN   Glyrol
CN   Glysanin
CN   IFP
CN   Incorporation factor
CN   Mackstat H 66
CN   NSC 9230
CN   Osmoglyn
CN   Pricerine 9091
CN   Trihydroxypropane
CN   Tryhydroxypropane
AR   30918-77-5
FS   3D CONCORD
DR   8013-25-0, 37228-54-9, 75398-78-6, 78630-16-7, 29796-42-7, 30049-52-6
MF   C3 H8 O3
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB,
       CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB,
       DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2,
       ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB,
       IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*,
       PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER,
       TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
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    Other Sources:   DSL**, EINECS**, TSCA**, WHO
        (**Enter CHEMLIST File for up-to-date regulatory information)
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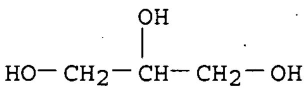

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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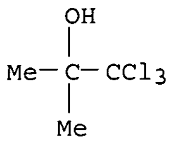
4901 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
52946 REFERENCES IN FILE CAPLUS (1947 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s e36
L17 1 57-15-8/BI

=> d

L17 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN **57-15-8** REGISTRY
CN 2-Propanol, 1,1,1-trichloro-2-methyl- (6CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .beta.,.beta.,.beta.-Trichloro-tert-butyl alcohol
CN 1,1,1-Trichloro-2-methyl-2-propanol
CN 1,1,1-Trichloro-tert-butyl alcohol
CN 2,2,2-Trichloro-1,1-dimethylethanol
CN 2-(Trichloromethyl)-2-propanol
CN Acetochlorone
CN Acetonchloroform
CN Acetone chloroform
CN Anhydrous chlorobutanol
CN Chlorbutanol
CN Chlorbutol
CN Chloreton
CN Chloretone
CN Chlorobutanol
CN Chlortran
CN Clortran
CN Coliquifilm
CN Dentalone
CN Khloreton
CN Methaform
CN NSC 44794
CN NSC 4596
CN NSC 5208
CN Sedaform
CN Trichloro-tert-butyl alcohol
CN Trichlorobutanol
FS 3D CONCORD
MF C4 H7 Cl3 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             843 REFERENCES IN FILE CA (1947 TO DATE)
               4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             843 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              30 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e37
L18          1 57-55-6/BI

=> d

L18  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   57-55-6  REGISTRY
CN   1,2-Propanediol (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   (.+-.)-1,2-Propanediol
CN   (.+-.)-Propylene glycol
CN   (RS)-1,2-Propanediol
CN   .alpha.-Propylene glycol
CN   1,2-(RS)-Propanediol
CN   1,2-Dihydroxypropane
CN   1,2-Propylene glycol
CN   1000PG
CN   2,3-Propanediol
CN   2-Hydroxypropanol
CN   DL-1,2-Propanediol
CN   dl-Propylene glycol
CN   Dowfrost
CN   Isopropylene glycol
CN   Methylethyl glycol
CN   Methylethylene glycol
CN   Monopropylene glycol
CN   NSC 69860
CN   PG 12
CN   Propylene glycol
CN   Sirlene
CN   Solar Winter Ban
CN   Solargard P
CN   Ucar 35
FS   3D CONCORD
DR   63625-56-9, 4254-16-4, 190913-75-8
MF   C3 H8 O2
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
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       CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB,
       DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2,
       ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB,
       IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PHAR, PIRA,
       PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, ULIDAT, USAN,
       USPAT2, USPATFULL, VETU, VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)
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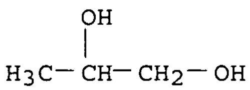

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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           20537 REFERENCES IN FILE CA (1947 TO DATE)
            2495 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           20585 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e38
L19          1 62-38-4/BI

=> d

L19   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN    62-38-4  REGISTRY
CN    Mercury, (acetato-.kappa.O)phenyl- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN    Mercury, (acetato)phenyl- (8CI)
CN    Mercury, (acetato-O)phenyl-
CN    Phenylmercury acetate (6CI)
OTHER NAMES:
CN    (Acetato-O)phenylmercury
CN    Acetatophenylmercury
CN    Acetic acid, phenylmercury deriv.
CN    Acetoxyphenylmercury
CN    Agrosan D
CN    Algimycin 200
CN    Anticon
CN    Antimucin WBR
CN    Antimucin WDR
CN    Benzene, (acetoxymercurio)-
CN    Bufen
CN    Bufen 30
CN    Ceresol
CN    Contra Creme
CN    Femma
CN    Fungicide R
CN    Fungitox OR
CN    Hexasan
CN    Hexasan (fungicide)
CN    Intercide 60
CN    Intercide PMA 18
CN    Liquiphene
CN    Lorophyn
CN    Meracen
CN    Mercron
CN    Mercuriphenyl acetate
CN    Mercuron
CN    Mergal A 25
CN    Mersolite 8
CN    Mersolite D
CN    Neantina
CN    Norforms
CN    NSC 35670
CN    NSC 61321
CN    Nuodex PMA 18
```

```
CN   Nylmerate
CN   Panomatic
CN   Parasan
CN   Parasan (bactericide)
CN   Phenylmercuric acetate
CN   Phix
CN   PMA
CN   PMA (fungicide)
CN   PMA 220
CN   PMAC
CN   PMAS
CN   Programin
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
     DISPLAY
DR   8013-47-6, 1337-06-0, 64684-45-3, 61840-45-7, 112415-59-5
MF   C8 H8 Hg O2
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS,
       CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU,
       EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE,
       MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO,
       TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)


AcO—Hg—Ph


            1691 REFERENCES IN FILE CA (1947 TO DATE)
              12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            1692 REFERENCES IN FILE CAPLUS (1947 TO DATE)
             208 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e39
L20          1 64-19-7/BI

=> d

L20  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   64-19-7  REGISTRY
CN   Acetic acid (7CI, 8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   acetic acid
CN   Aci-Jel
CN   E 260
CN   Ethanoic acid
CN   Ethanoic acid monomer
CN   Ethylic acid
CN   Glacial acetic acid
CN   Methanecarboxylic acid
CN   NSC 111201
CN   NSC 112209
CN   NSC 115870
CN   NSC 127175
CN   NSC 132953
CN   NSC 406306
CN   Vinegar acid
FS   3D CONCORD
DR   77671-22-8
MF   C2 H4 O2
```

```
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB,
       CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB,
       DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2,
       ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB,
       IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PIRA,
       PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2,
       USPATFULL, VETU, VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)
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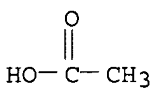

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

           78385 REFERENCES IN FILE CA (1947 TO DATE)
            3681 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           78503 REFERENCES IN FILE CAPLUS (1947 TO DATE)
               2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e409
'E409' NOT FOUND
The E# entered is not currently defined.

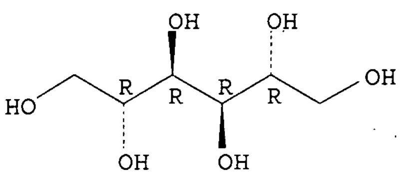
=> s e40
L21             1 69-65-8/BI

=> d

L21  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   69-65-8  REGISTRY
CN   D-Mannitol (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Cordycepic acid (6CI, 7CI)
CN   Mannitol, D- (8CI)
OTHER NAMES:
CN   D-(-)-Mannitol
CN   Diosmol
CN   Isotol
CN   Manicol
CN   Maniton S
CN   Manna sugar
CN   Mannidex
CN   Mannigen
CN   Mannistol
CN   Mannit
CN   Mannit-P
CN   Mannite
CN   Mannitol
CN   Mannitolum
CN   Mannogem 2080
CN   Marine Crystal
CN   Osmitrol
CN   Osmosal
CN   Resectisol
FS   STEREOSEARCH
```

```
DR   123897-58-5, 75398-80-0, 85085-15-0
MF   C6 H14 O6
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS,
       CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES,
       DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA,
       MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PHARMASEARCH,
       PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, USAN, USPAT2,
       USPATFULL, VETU
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.
```

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

           12642 REFERENCES IN FILE CA (1947 TO DATE)
             287 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           12660 REFERENCES IN FILE CAPLUS (1947 TO DATE)
               2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e41
L22           1 7647-01-0/BI

=> d

L22  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   7647-01-0  REGISTRY
CN   Hydrochloric acid (6CI, 7CI, 8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Anhydrous hydrochloric acid
CN   Chloridric acid
CN   Chlorohydric acid
CN   Dilute hydrochloric acid
CN   Enplate PO 236
CN   Hydrochloric acid gas
CN   Hydrogen chloride
CN   Hydrogen chloride (HCl)
CN   Muriatic acid
CN   NSC 77365
DR   113962-65-5, 51005-19-7, 61674-62-2, 218625-68-4
MF   Cl H
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN,
       CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DETHERM*,
       DIOGENES, DIPPR*, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2,
       GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS,
       NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA,
       ULIDAT, USAN, USPAT2, USPATFULL, VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
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         (**Enter CHEMLIST File for up-to-date regulatory information)


HCl

           78321 REFERENCES IN FILE CA (1947 TO DATE)
             466 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           78412 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              40 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e42
L23          1 7647-14-5/BI

=> d

L23  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   7647-14-5  REGISTRY
CN   Sodium chloride (NaCl) (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Salt (6CI, 7CI)
CN   Sodium chloride (8CI)
OTHER NAMES:
CN   Adsorbanac
CN   Ayr
CN   BCD
CN   Brinewate Superfine
CN   Common salt
CN   Iodized salt
CN   Mafiron
CN   Natrum mur
CN   NSC 77364
CN   Sea salt
CN   Sodium monochloride
CN   Special Salt 100/95
CN   SS Salt
CN   Table salt
CN   Titrisol
CN   Uzushio Biryuu M
CN   Watesal A
DR   8028-77-1, 11062-32-1, 11062-43-4, 418758-90-4
MF   Cl Na
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN,
       CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*,
       DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT,
       ENCOMPPAT2, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*,
       MSDS-OHS, NIOSHTIC, PDLCOM*, PHARMASEARCH, PIRA, PROMT, RTECS*,
       TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)


Cl—Na

          111185 REFERENCES IN FILE CA (1947 TO DATE)
             361 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
          111306 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              75 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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```
=> s e43
L24          1 77-92-9/BI

=> d

L24  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   77-92-9  REGISTRY
CN   1,2,3-Propanetricarboxylic acid, 2-hydroxy- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Citric acid (8CI)
OTHER NAMES:
CN   2-Hydroxy-1,2,3-propanetricarboxylic acid
CN   3-Carboxy-3-hydroxypentane-1,5-dioic acid
CN   Aciletten
CN   Chemfill
CN   Citretten
CN   Citro
CN   E 330
CN   F 0001 (polycarboxylic acid)
CN   Hydrocerol A
CN   NSC 112226
CN   NSC 30279
CN   NSC 626579
CN   Suby G
CN   Uro-trainer
FS   3D CONCORD
DR   12262-73-6, 43136-35-2, 245654-34-6
MF   C6 H8 O7
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB,
       CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,
       DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2,
       ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB,
       IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*,
       PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER,
       TULSA, USAN, USPAT2, USPATFULL, VETU, VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)
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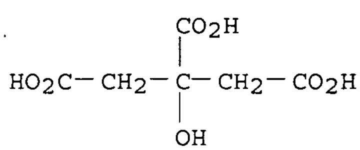


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

          44327 REFERENCES IN FILE CA (1947 TO DATE)
           2635 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
          44392 REFERENCES IN FILE CAPLUS (1947 TO DATE)
              9 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e44
L25          1 7724-38-1/BI

=> d
```

```
L9   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   13072-89-4  REGISTRY
CN   6,10-Epoxy-4,8,11a-metheno-11aH-oxocino[4,3-f][1,3,5]oxadiazepine-6,9,11-
     triol, 2-amino-1,4,5a,6,8,9,10,11-octahydro-9-(hydroxymethyl)-,
     (4S,5aS,6S,8R,9S,10S,11S,11aR,12R)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Tetrodotoxin, 4,9-anhydro- (8CI)
CN   Tetrodotoxin, 4,9-dideoxy-4,9-epoxy-, (4.beta.,9.beta.)-
CN   Tetrodotoxin, anhydro- (7CI)
OTHER NAMES:
CN   4,9-Anhydrotetrodotoxin
CN   Anhydroepitetrodotoxin
CN   Anhydrotetrodotoxin
FS   STEREOSEARCH
DR   7724-36-9, 16998-61-1, 17289-89-3, 2054-43-5
MF   C11 H15 N3 O7
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS,
       CASREACT, MEDLINE, NAPRALERT, RTECS*, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
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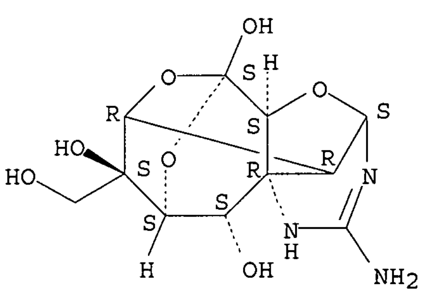
Absolute stereochemistry.

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

              89 REFERENCES IN FILE CA (1947 TO DATE)
              89 REFERENCES IN FILE CAPLUS (1947 TO DATE)
               3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> d sel
E1             4      KANG XUEZHEN/AU
E2             1      KANG XULIANG/AU
E3            73      KANG Y/AU
E4             2      KANG Y A/AU
E5             4      KANG Y B/AU
E6            45      KANG Y C/AU
E7             1      KANG Y F/AU
E8            11      KANG Y G/AU
E9            62      KANG Y H/AU
E10            2      KANG Y I/AU
E11            9      KANG Y J/AU
E12           56      KANG Y JAMES/AU
E13            1      KANG YUFAN/AU
E14            2      KANG YUFEN/AU
E15            1      KANG YUHONG/AU
E16            2      KANG YUHUA/AU
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            433 REFERENCES IN FILE CAPLUS (1947 TO DATE)


=> s e30
L11             1 14265-44-2/BI

=> d

L11  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   14265-44-2  REGISTRY
CN   Phosphate (8CI, 9CI)   (CA INDEX NAME)
OTHER NAMES:
CN   Orthophosphate
CN   Orthophosphate (PO43-)
CN   Orthophosphate(3-)
CN   Phosphate (PO43-)
CN   Phosphate anion(3-)
CN   Phosphate ion (PO43-)
CN   Phosphate ion(3-)
CN   Phosphate trianion
CN   Phosphate(3-)
CN   Phosphoric acid, ion(3-)
FS   3D CONCORD
DR   264888-19-9
MF   O4 P
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN,
       CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA,
       NIOSHTIC, PIRA, PROMT, TOXCENTER, TULSA, ULIDAT, USPAT2, USPATFULL,
       VETU, VTB
         (*File contains numerically searchable property data)
     Other Sources:   NDSL**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)
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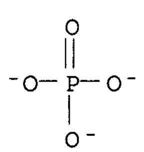

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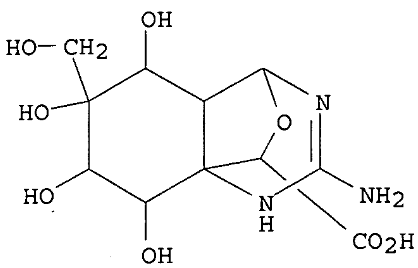
          33853 REFERENCES IN FILE CA (1947 TO DATE)
            306 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
          33883 REFERENCES IN FILE CAPLUS (1947 TO DATE)


=> s e31
L12             1 3270-35-7/BI

=> d

L12  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   3270-35-7  REGISTRY
CN   1H-4,8a-(Epoxymethano)quinazoline-9-carboxylic acid, 2-amino-4,4a,5,6,7,8-
     hexahydro-5,6,7,8-tetrahydroxy-6-(hydroxymethyl)-,
     (4S,4aR,5R,6S,7R,8R,8aR,9R)- (9CI)   (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H-4,8a-(Epoxymethano)quinazoline-9-carboxylic acid, 2-amino-4,4a,5,6,7,8-
     hexahydro-5,6,7,8-tetrahydroxy-6-(hydroxymethyl)-, [4S-
     (4.alpha.,4a.beta.,5.alpha.,6.beta.,7.beta.,8.beta.,8a.alpha.,9S*)]-
```

CN   Tetrodonic acid (7CI, 8CI)
MF   C11 H17 N3 O8
CI   COM
LC   STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAOLD, CAPLUS, MEDLINE, NAPRALERT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

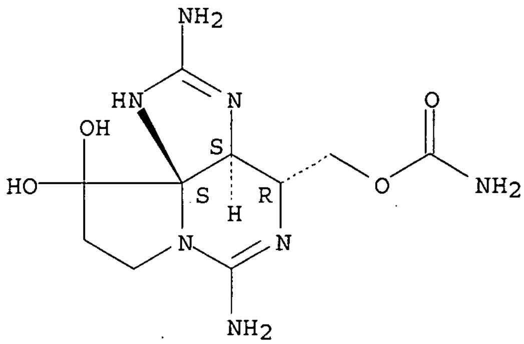
31 REFERENCES IN FILE CA (1947 TO DATE)
31 REFERENCES IN FILE CAPLUS (1947 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s e32
L13   1 35523-89-8/BI

=> d

L13 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN   **35523-89-8** REGISTRY
CN   1H,10H-Pyrrolo[1,2-c]purine-10,10-diol, 2,6-diamino-4-[[(aminocarbonyl)oxy]methyl]-3a,4,8,9-tetrahydro-, (3aS,4R,10aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H,10H-Pyrrolo[1,2-c]purine-10,10-diol, 2,6-diamino-4-[[(aminocarbonyl)oxy]methyl]-3a,4,8,9-tetrahydro-, [3aS-(3a.alpha.,4.alpha.,10aR*)]-
CN   Saxitoxin (7CI, 8CI)
OTHER NAMES:
CN   (+)-Saxitoxin
CN   Saxitoxin hydrate
CN   STX
FS   STEREOSEARCH
DR   11017-04-2, 55803-44-6, 51938-46-6
MF   C10 H17 N7 O4
CI   COM
LC   STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CEN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, NAPRALERT, NIOSHTIC, PROMT, RTECS*, TOXCENTER, ULIDAT, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             851 REFERENCES IN FILE CA (1947 TO DATE)
              38 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             853 REFERENCES IN FILE CAPLUS (1947 TO DATE)
               4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e33
L14          1 4368-28-9/BI

=> d

L14  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   4368-28-9  REGISTRY
CN   5,9:7,10a-Dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-4,7,10,11,12-
     pentol, octahydro-12-(hydroxymethyl)-2-imino-,
     (4R,4aR,5R,7S,9S,10S,10aR,11S,12S)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   8a(1H)-Quinazolineorthoglycolic acid, octahydro-4,5,6,7,8-pentahydroxy-6-
     (hydroxymethyl)-2-imino-, cyclic 8a,5:8a,7-ester (7CI)
CN   Tetrodotoxin (8CI)
OTHER NAMES:
CN   (-)-Tetrodotoxin
CN   5,9:7,10a-Dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-4,7,10,11,12-
     pentol, octahydro-12-(hydroxymethyl)-2-imino-, [4R-
     (4.alpha.,4a.alpha.,5.alpha.,7.alpha.,9.alpha.,10.alpha.,10a.beta.,11S*,12
     S*)]-
CN   Araregai toxin
CN   Babylonia japonica toxin 1
CN   BJT 1
CN   Maculotoxin
CN   Spheroidine
CN   Tarichatoxin
CN   Tetrodotoxine
CN   TTX
CN   [4R-(4.alpha.,4a.alpha.,5.alpha.,7.alpha.,9.alpha.,10.alpha.,10a.beta.,11S
     *,12S*)]-Octahydro-12-(hydroxymethyl)-2-imino-5,9:7,10a-dimethano-10aH-
     [1,3]dioxocino[6,5-d]pyrimidine-4,7,10,11,12-pentol
FS   STEREOSEARCH
DR   12626-86-7, 9014-39-5, 11005-69-9, 11026-09-8, 17289-88-2, 2229-61-0
MF   C11 H17 N3 O8
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS,
       CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT,
       IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PROMT, RTECS*,
       TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
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L25  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   7724-38-1  REGISTRY
CN   5,9:7,10a-Dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-7,10,11,12-
     tetrol, 4-aminooctahydro-12-(hydroxymethyl)-2-imino-,
     (4R,4aR,5R,7S,9S,10S,10aR,11S,12S)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Tetrodotoxin, 4-amino-4-deoxy-, (4.alpha.)- (8CI)
OTHER NAMES:
CN   4-Aminodeoxytetrodotoxin
CN   Tetrodaminotoxin
FS   STEREOSEARCH
DR   16998-62-2, 17289-94-0, 2054-84-4
MF   C11 H18 N4 O7
LC   STN Files:   BEILSTEIN*, CA, CAOLD, CAPLUS, RTECS*, TOXCENTER, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
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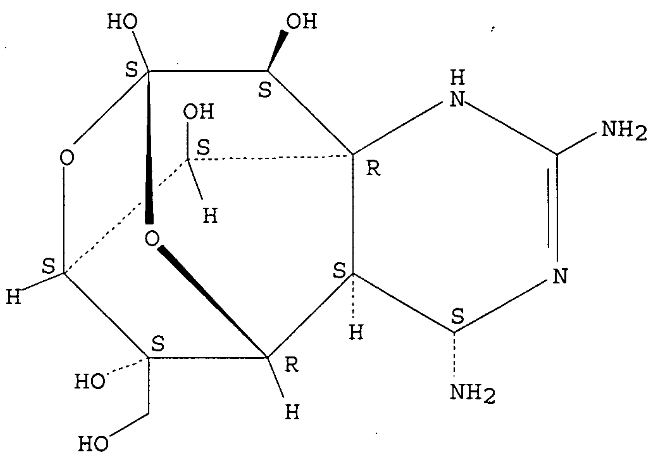


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               1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e45
L26          1 7724-39-2/BI

=> d

L26  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   7724-39-2  REGISTRY
CN   5,9:7,10a-Dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-7,10,11,12-
     tetrol, octahydro-12-(hydroxymethyl)-2-imino-4-methoxy-,
     (4R,4aR,5R,7S,9S,10S,10aR,11S,12S)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Tetrodotoxin, O4-methyl-
OTHER NAMES:
CN   4-Methoxytetrodotoxin
CN   4-O-Methyltetrodotoxin
CN   Methoxytetrodotoxin
FS   STEREOSEARCH
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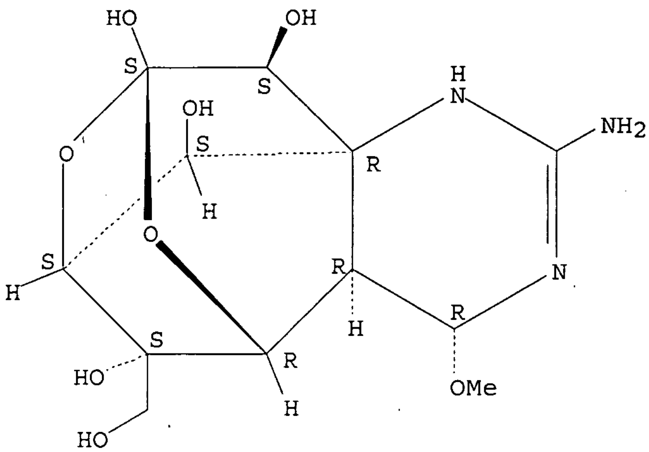
DR   16846-38-1, 17289-93-9
MF   C12 H19 N3 O8
LC   STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, RTECS*, TOXCENTER, USPAT2,
      USPATFULL
        (*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

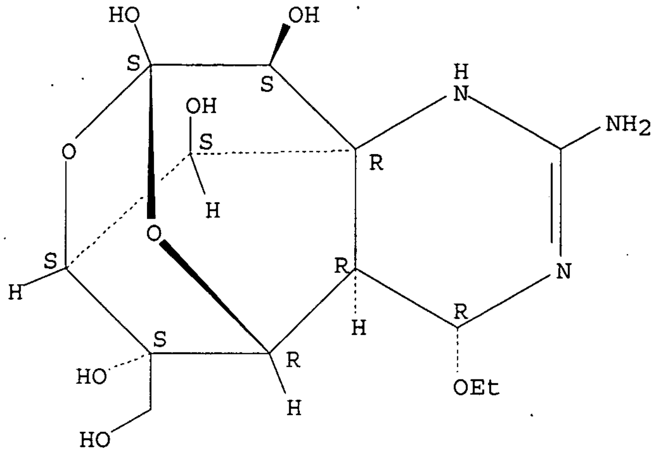
              10 REFERENCES IN FILE CA (1947 TO DATE)
              10 REFERENCES IN FILE CAPLUS (1947 TO DATE)
               1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s e46
L27   1 7724-40-5/BI

=> d

L27   ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN   **7724-40-5** REGISTRY
CN   5,9:7,10a-Dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-7,10,11,12-
      tetrol, 4-ethoxyoctahydro-12-(hydroxymethyl)-2-imino-,
      (4R,4aR,5R,7S,9S,10S,10aR,11S,12S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Tetrodotoxin, O4-ethyl- (7CI, 8CI)
OTHER NAMES:
CN   4-Ethoxytetrodotoxin
CN   Ethoxytetrodotoxin
FS   STEREOSEARCH
DR   16846-39-2
MF   C13 H21 N3 O8
LC   STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, RTECS*, TOXCENTER, USPAT2,
      USPATFULL
        (*File contains numerically searchable property data)

Absolute stereochemistry.



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               3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> s e47
L28          1 7724-41-6/BI

=> d

L28  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   7724-41-6  REGISTRY
CN   5,9:7,10a-Dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-7,10,11,12-
     tetrol, 2-amino-1,4,4a,5,9,10-hexahydro-12-(hydroxymethyl)-,
     (4aR,5R,7S,9S,10S,10aR,11S,12S)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   5,9:7,10a-Dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-7,10,11,12-
     tetrol, octahydro-12-(hydroxymethyl)-2-imino-, [4aR-
     (4a.alpha.,5.alpha.,7.alpha.,9.alpha.,10.alpha.,10a.beta.,11S*,12S*)]-
CN   Tetrodotoxin, 4-deoxy- (8CI)
CN   Tetrodotoxin, deoxy- (7CI)
OTHER NAMES:
CN   Deoxytetrodotoxin
CN   Desoxytetrodotoxin
FS   STEREOSEARCH
DR   16813-05-1, 17289-92-8
MF   C11 H17 N3 O7
LC   STN Files:  BEILSTEIN*, CA, CAOLD, CAPLUS, IFICDB, IFIPAT, IFIUDB,
       RTECS*, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
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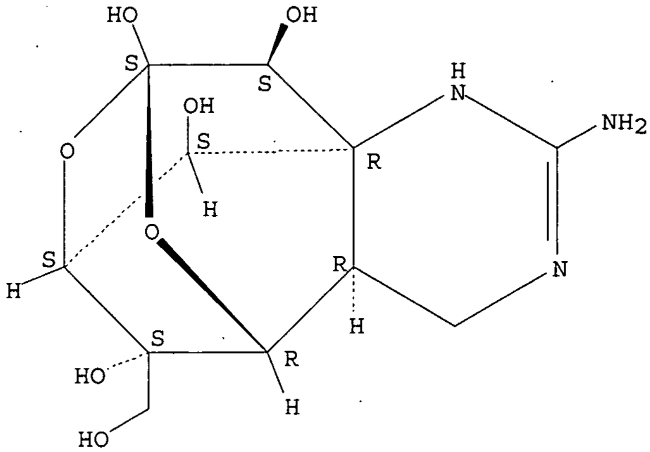

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YRIGHT 2003 ACS on STN

AN 1997:780599 CAPLUS
DN 128:200981
TI Dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine
AU Anagnostakis, Yannis; Kastellakis, Andreas; Spyraki, Christina
CS Heraklion, P.O. Box 1393, School of Medicine, Department of Basic Sciences, Laboratory of Pharmacology, University of Crete, Crete, 71110, Greece
SO European Neuropsychopharmacology (1998), 8(1), 47-53
CODEN: EURNE8; ISSN: 0924-977X
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-11 (Pharmacology)
AB It has been hypothesized that the intrapallidal morphine-induced dopamine release in the nucleus accumbens may be mediated by thalamocorticostriatal or mesolimbic pathways. To challenge the above hypothesis, the authors examd. whether changes in accumbal dopamine and its metabolites produced by intrapallidal morphine (a) are assocd. with local excitatory amino acid neurotransmission (b) are detd. by impulse propagation in dopamine neurons and (c) are obsd. both ipsi- and contralateral to the morphine administration site. In vivo microdialysis was used to assess dopamine release and metab. in the right and the left nucleus accumbens sep. of awake, unrestrained rats. Vehicle or **morphine** hydrochloride (10 .mu.l/26.0 mM) was applied unilaterally into the pallidum alone or in **combination** with ipsilateral application of the N-methyl-d-aspartate (NMDA) receptor antagonist dizocilpine (MK-801) into the nucleus accumbens or the sodium channel blocker **tetrodotoxin** into the medial forebrain bundle. Drugs' application was performed via reverse dialysis. Concns. of dopamine, 3,4-dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) in the collected dialyzate were measured by high performance liq. chromatog. with electrochem. detection. Morphine administration resulted in elevated levels of dopamine in the ipsilateral and of DOPAC and HVA in both the ipsi and contralateral nucleus accumbens. Dizocilpine (MK-801) (0.3 mM) did not influence the basal levels of dopamine, DOPAC or HVA in the nucleus accumbens. Ipsilaterally, dizocilpine (MK-801) inhibited the effect of morphine on dopamine release, whereas it increased significantly the effect of the drug on DOPAC and HVA. Tetrodotoxin (3 .mu.M) reversed the effect of intrapallidal morphine on dopamine, DOPAC or HVA in the ipsilateral nucleus accumbens. The results show that the intrapallidal morphine-induced dopaminergic activation in the ipsilateral nucleus accumbens is dependent upon both phasic and tonic activation of dopaminergic neurons. They suggest that both the thalamocorticostriatal and the mesolimbic dopamine pathways may mediate the investigated effect of morphine.
ST intrapallidal morphine dopamine release nucleus accumbens
IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NMDA-binding; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)
IT Nerve
(dopaminergic; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)
IT Brain
(mesolimbic dopaminergic system; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)
IT Brain
(nucleus accumbens; dizocilpine (MK-801) and tetrodotoxin influence

accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT Brain
(thalamocorticostriatal dopaminergic pathway; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT 57-27-2, Morphine, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT 51-61-6, Dopamine, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT 102-32-9, 3,4-Dihydroxyphenyl acetic acid 306-08-1, Homovanillic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Albanese, A; J Comp Neurol 1983, V216, P406 MEDLINE
(2) Alheid, G; Neuroscience 1988, V27, P1 MEDLINE
(3) Anagnostakis, Y; Brain Res Bull 1994, V34, P275 CAPLUS
(4) Barbeito, L; Eur J Neurosci 1990, V2, P304
(5) Berendse, H; J Comp Neurol 1992, V316, P314 MEDLINE
(6) Carlsson, A; Eur Neuropsychopharmacol 1995, V5, P160
(7) Carpenter, M; The Basal Ganglia Advances in Behavioral Biology 1984, P1
(8) Carter, D; J Comp Neurol 1978, V177, P113 MEDLINE
(9) Carter, D; Neuroscience 1977, V2, P569 MEDLINE
(10) Christie, M; Brain Res 1985, V333, P169 MEDLINE
(11) Chronister, R; Neurosci Lett 1980, V17, P231 MEDLINE
(12) Clow, D; J Pharmacol Exp Ther 1989, V248, P722 CAPLUS
(13) Di Chiara, G; Proc Natl Acad Sci 1988, V85, P5274 CAPLUS
(14) Glowinski, J; Trends Neurosci 1984, V7, P415
(15) Grace, A; Neuroscience 1991, V41, P1 CAPLUS
(16) Groenewegen, H; Neuroscience 1993, V57, P113 MEDLINE
(17) Groenewegen, H; The Mesolimbic Dopamine System:From Motivation to Action 1990, P19
(18) Herkenham, M; J Comp Neurol 1979, V183, P487 MEDLINE
(19) Huettner, J; Proc Natl Acad Sci

L100 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2002:905867 CAPLUS

DN 137:363099

TI Analgesic composition and method

IN Ku, Baoshan; Shum, Frank Hay Kong

PA Wex Medical Instrumentation Co., Ltd., Peop. Rep. China

SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-517
ICS A61K031-485; A61P025-04

CC 1-11 (Pharmacology)
Section cross-reference(s): 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002094272	A1	20021128	WO 2002-CN339	20020520

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	CN 1386505	A	20021225	CN 2001-118098	20010518
	US 2002198226	A1	20021226	US 2002-62483	20020205
PRAI	CN 2001-118098	A	20010518		

AB A pharmaceutical analgesic compn. comprising an opioid analgesic agent and a compd. that binds to the SS1 or SS2 subunit of a sodium channel, such as tetrodotoxin and saxitoxin, and analogs thereof. Administration of an opioid analgesic agent and a compd. that binds to the SS1 or SS2 subunit of a sodium channel, such as tetrodotoxin and saxitoxin, and their analogs, produces analgesia in the treatment of pain in mammals. For example, the synergistic analgesia effect produced by co-administering tetrodotoxin (TTX) and morphine was obsd. in a formalin test in rats. Morphine used alone at 0.30 mg/kg only produced 10.2% inhibition of formalin-induced pain. Combination of TTX at 0.19 .mu.g/kg with morphine at 2.50 mg/kg increased the inhibition rate to 86.7% from 34.9% where the latter was used alone. TTX at a dose of 0.39 .mu.g/kg (1/50 of LD50) produced an inhibition rate of 32.9% when used alone and 66.2% in combination with 0.15 mg/kg of morphine, whereas the latter only produced an inhibition rate of 7.2% when used alone.

ST opioid sodium channel blocker injection synergistic analgesic

IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SS1 or SS2 subunit; synergistic analgesic activity of combination of opioid and sodium channel blocker)

IT Drug delivery systems
(injections, i.m.; synergistic analgesic activity of combination of opioid and sodium channel blocker)

IT Drug delivery systems
(injections, intrathecal; synergistic analgesic activity of combination of opioid and sodium channel blocker)

IT Ion channel blockers
(sodium; synergistic analgesic activity of combination of opioid and sodium channel blocker)

IT Analgesics
(synergistic analgesic activity of combination of opioid and sodium

channel blocker)

IT Opioids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic analgesic activity of combination of opioid and sodium channel blocker)

IT Drug interactions
(synergistic; synergistic analgesic activity of combination of opioid and sodium channel blocker)

IT 52-26-6, Morphine hydrochloride 57-27-2, Morphine, biological studies 76-57-3, Codeine 76-99-3, Methadone 437-38-7, Fentanyl **3270-35-7**, Tetrodonic acid **4368-28-9**, **Tetrodotoxin 7724-38-1**, Tetrodaminotoxin **7724-39-2**, **Methoxytetrodotoxin 7724-40-5**, **Ethoxytetrodotoxin 7724-41-6**, **Deoxytetrodotoxin 13072-89-4**, **Anhydrotetrodotoxin 35523-89-8**, Saxitoxin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic analgesic activity of **combination** of **opioid** and sodium channel blocker)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Anon; US 4022899 1977 CAPLUS
(2) Anon; CN 1145225 A 1997 CAPLUS
(3) Xur, Y; JIANGSU CLINICAL MEDICAL JOURNAL 2001, V5(5), P361

L39 ANSWER 4 OF 4 CAPLUS

AN 1976:586486 CAPLUS

DN 85:186486

TI The effect of metoclopramide on intestinal muscle responses and the peristaltic reflex in vitro

AU Okwuasaba, Francis K.; Hamilton, John T.

CS Dep. Pharmacol., Univ. West. Ontario, London, ON, Can.

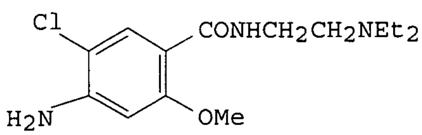
SO Canadian Journal of Physiology and Pharmacology (1976), 54(3), 393-404
CODEN: CJPPA3; ISSN: 0008-4212

DT Journal

LA English

CC 1-4 (Pharmacodynamics)

GI



HCl I

AB In isolated guinea pig ileum and taenia coli, rabbit ileum, and rat duodenum, metoclopramide-HCl (I) (0.1 or 1.0 .mu.M) increased the tone and response to acetylcholine, carbachol and nicotine: had no effect on responses to histamine, KCl, and prostaglandin E1; and decreased responses to 5-hydroxytryptamine (5-HT). Atropine, methysergide, **morphine**, and **tetrodotoxin**, alone or in **combination**, partially blocked the stimulatory responses to I, but hexamethonium, mepyramine, and indomethacin did not. I (1.0 mM) lowered the threshold for elicitation of the peristaltic reflex to a subthreshold intraluminal pressure (2.5 cm water), facilitated the peristaltic response to threshold pressures (3-4 cm water), and restored the reflex in fatigued prepns., but not that depressed by cooling to 24.degree.. During block of peristalsis by atropine, hexamethonium, or methysergide (applied serosally), 5-HT (0.25 .mu.M) but not I (1.0 .mu.M) effectively restored the peristaltic reflex, but neither antagonized the inhibition by morphine or procaine acting serosally. However, I (1.0 .mu.M) reestablished peristalsis inhibited by a high concn. of 5-HT (4 .times. 10 .mu.M). These results do not support the hypothesis that the stimulatory action of I is entirely dependent on either peripheral sensitization of muscarinic receptors or an action on tryptaminergic mechanisms, but are consistent with the previous conclusion that an addnl. component may be a blockade of some intrinsic inhibitory (possibly purinergic) substance normally restraining intestinal motility or tone.

ST metoclopramide intestine contraction; peristalsis metoclopramide

IT Intestine
(contraction and motility of, metoclopramide effect on)

=>

L39 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:780599 CAPLUS

DN 128:200981

TI Dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine

AU Anagnostakis, Yannis; Kastellakis, Andreas; Spyraki, Christina

CS Heraklion, P.O. Box 1393, School of Medicine, Department of Basic Sciences, Laboratory of Pharmacology, University of Crete, Crete, 71110, Greece

SO European Neuropsychopharmacology (1998), 8(1), 47-53
CODEN: EURNE8; ISSN: 0924-977X

PB Elsevier Science B.V.

DT Journal

LA English

CC 1-11 (Pharmacology)

AB It has been hypothesized that the intrapallidal morphine-induced dopamine release in the nucleus accumbens may be mediated by thalamocorticostriatal or mesolimbic pathways. To challenge the above hypothesis, the authors examd. whether changes in accumbal dopamine and its metabolites produced by intrapallidal morphine (a) are assocd. with local excitatory amino acid neurotransmission (b) are detd. by impulse propagation in dopamine neurons and (c) are obsd. both ipsi- and contralateral to the morphine administration site. In vivo microdialysis was used to assess dopamine release and metab. in the right and the left nucleus accumbens sep. of awake, unrestrained rats. Vehicle or **morphine** hydrochloride (10 .mu.l/26.0 mM) was applied unilaterally into the pallidum alone or in **combination** with ipsilateral application of the N-methyl-d-aspartate (NMDA) receptor antagonist dizocilpine (MK-801) into the nucleus accumbens or the sodium channel blocker **tetrodotoxin** into the medial forebrain bundle. Drugs' application was performed via reverse dialysis. Concns. of dopamine, 3,4-dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) in the collected dialyzate were measured by high performance liq. chromatog. with electrochem. detection. Morphine administration resulted in elevated levels of dopamine in the ipsilateral and of DOPAC and HVA in both the ipsi and contralateral nucleus accumbens. Dizocilpine (MK-801) (0.3 mM) did not influence the basal levels of dopamine, DOPAC or HVA in the nucleus accumbens. Ipsilaterally, dizocilpine (MK-801) inhibited the effect of morphine on dopamine release, whereas it increased significantly the effect of the drug on DOPAC and HVA. Tetrodotoxin (3 .mu.M) reversed the effect of intrapallidal morphine on dopamine, DOPAC or HVA in the ipsilateral nucleus accumbens. The results show that the intrapallidal morphine-induced dopaminergic activation in the ipsilateral nucleus accumbens is dependent upon both phasic and tonic activation of dopaminergic neurons. They suggest that both the thalamocorticostriatal and the mesolimbic dopamine pathways may mediate the investigated effect of morphine.

ST intrapallidal morphine dopamine release nucleus accumbens

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NMDA-binding; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT Nerve
(dopaminergic; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT Brain
(mesolimbic dopaminergic system; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT Brain

(nucleus accumbens; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT Brain
(thalamocorticostriatal dopaminergic pathway; dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT 57-27-2, Morphine, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT 51-61-6, Dopamine, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

IT 102-32-9, 3,4-Dihydroxyphenyl acetic acid 306-08-1, Homovanillic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(dizocilpine (MK-801) and tetrodotoxin influence accumbal dopamine release evoked by intrapallidal morphine in relation to dopaminergic pathways and NMDA receptors)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

L5 ANSWER 7 OF 7 USPATFULL on STN

SUMM The present invention includes methods of producing long-lasting local anesthesia, comprising administering a pharmaceutically acceptable composition of a long-acting sodium channel blocking compound, wherein said compound binds to the extracellular mouth of the sodium channel, occluding the channel by a mechanism separate from that of local anesthetics, such as proparacaine. Preferably, such methods achieve local anesthesia of long duration, lasting at least 3 hours (3 to 10 hours), preferably at least 4 hours (4-10 hours), and most preferably at least 6 to 10 hours. Preferred compounds include toxins or analogs thereof that specifically bind to a site formed in part by an extracellular region of the alpha subunit of a sodium channel. Most preferred compounds comprise the class of toxins and analogs that specifically bind to a site formed by the **SS1** and **SS2** extracellular regions of the alpha subunit of a **sodium channel**, wherein such compounds include tetrodotoxin, saxitoxin and analogs thereof. Surprisingly, these long-acting sodium channel blocking compounds, which are well known, potent neurotoxins, provide long-lasting local anesthesia without inhibiting reepithelialization.

CLM What is claimed is:

5. The method of claim 4, wherein said site is on an **SS2** extracellular region of a **sodium channel** alpha subunit.

16. The method of claim 15, wherein said long-acting sodium channel blocking compound is a compound capable of specifically binding to a site on an extracellular region of a **sodium channel** alpha subunit, wherein said site is on either an **SS1** region or an SS2 region.

L12 ANSWER 1 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB To effectively manage the application of pesticides, diagnostic means to monitor the frequency of resistant alleles in pest populations is fundamental and a crit. need. Such diagnostic techniques must be cheap, rapid, rugged, and be of high enough resoln. to identify heterozygote individuals. Clearly, DNA-based diagnostic procedures have many of these attributes and their development is rapidly expanding. Two DNA-based genotyping techniques, bi-directional PCR amplification of specific allele (bi-PASA) and single stranded conformational polymorphism (**SSCP**), have been developed and validated in field trials. Recently, two point mutations, T929I and L932F, located in the IIS5 transmembrane segment of the voltage-sensitive **sodium channel** alpha **subunit** gene, have been identified and found assocd. with permethrin resistance (kdr-type) in the human head louse, Pediculus capitis. Using a serial invasive signal amplification reaction (SISAR) method, we have now simultaneously detected both mutations, in both homozygote and heterozygote individuals, in spite of their close proximity.

L12 ANSWER 2 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB Mutations in the alpha 1 **subunit** of the voltage-gated **sodium channel** (SCN1A) have been increasingly recognized as an important cause of familial epilepsy in humans. However, the functional consequences of these mutations remain largely unknown. The authors identified a mutation (D188V) in SCN1A segregating with generalized epilepsy with febrile seizures (GEFS) in a large kindred. Compared to wild-type sodium channels, in vitro expression of channels harboring the D188V mutation were found to be more resistant to the decline in amplitude that is normally obsd. over the course of high frequency pulse trains. This small change on a single aspect of channel function is compatible with an increase in membrane excitability, such as during sustained and uncontrolled neuronal discharges. These data suggest that this specific effect on sodium channel function could be a general mechanism in the pathophysiol. of epilepsies caused by mutations in sodium channels in humans.

IT Human
Mutation
  SSCP (single-strand conformation polymorphism)
   (gene SCN1A D188V mutation causing generalized epilepsy with febrile seizures plus)

L12 ANSWER 3 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB A method of identifying a subject predisposed to a disorder assocd. with ion channel dysfunction comprises ascertaining whether at least one of the genes encoding ion channel subunits in said subject has undergone a mutation event. The invention is based on a new genetic model postulating that idiopathic generalized epilepsies (IGEs) and generalized epilepsy with febrile seizures plus (GEFS+) are due to the combination of two mutations in multi-subunit ion channels. A no. of novel mutations or variants are identified in genes encoding subunits of ion channels in individuals with epilepsy using **SSCP** anal. and sequencing. Specific mutations included R396C, R369Q, and P474R in the CHRNA4 subunit and T26M, L301V, V308A, and G412D in the CHRNB2 subunit of human nicotinic acetylcholine receptor.

ST ion channel gene mutation epilepsy diagnosis therapy; sequence ion channel gene mutation epilepsy; nicotinic acetylcholine channel mutation epilepsy; **sodium channel subunit** mutation epilepsy

IT **SSCP** (single-strand conformation polymorphism)
   (diagnosis by; mutations in human ion channels assocd. with epilepsy and other disorders and their diagnostic and therapeutic uses)

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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PI   WO 2003008574      A1    20030130        WO 2002-AU910    20020708
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
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L12 ANSWER 4 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB The present invention relates to the use of combinations of sodium channel blocking compds. and aspirin in manufg. drugs for producing synergistically analgesic effect in mammals, in which said compds. bind to .alpha.-**subunit** of **SS1** or **SS2** sites in the **sodium channel**. According to the invention, pharmaceutical compns. have enhancing analgesic effect, and therefore dosage of aspirin as well as its side effects would be reduced.

IT **Sodium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.-**subunit** of **SS1** or **SS2**; use of **sodium channel** blockers and aspirin in manufg. drugs for producing analgesia synergistically in mammals)

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     PATENT NO.         KIND  DATE            APPLICATION NO.  DATE
     ---------------    ----  --------        ---------------  --------
PI   WO 2003000268      A1    20030103        WO 2002-CN428    20020618
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CO,
             CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
             HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
             UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CN 1393223         A     20030129        CN 2001-115990   20010622
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L12 ANSWER 5 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Single-strand conformational polymorphism analysis (**SSCP**) and sequencing for ion channel gene mutations

AB The combined use of DNA screening and single-strand conformational polymorphism (**SSCP**) to identify gene mutations has been shown to be more cost efficient. This is esp. true for screening a large no. of samples, if the gene of interest has many exons and the majority of mutations are novel. Some good examples are ion channel genes such as the .alpha.1A-subunit of the P/Q-type calcium channel gene, CACNA1A, and the skeletal muscle .alpha.1-**subunit** of the **sodium channel** gene, SCN4A, which consist of 47 and 24 exons, resp. Protocols are presented for **SSCP** anal. and for DNA sequencing.

ST **SSCP** DNA screening ion channel gene mutation; polymorphism screening sodium calcium ion channel gene

IT Gene, animal
RL: ANT (Analyte); ANST (Analytical study)
(CACNA1A, screening for mutation in; single-strand conformational polymorphism anal. (**SSCP**) and sequencing for ion channel gene mutations)

IT Gene, animal
RL: ANT (Analyte); ANST (Analytical study)
(SCN4A, screening for mutation in; single-strand conformational polymorphism anal. (**SSCP**) and sequencing for ion channel gene mutations)

IT Mutation
(detection of; single-strand conformational polymorphism anal. (**SSCP**) and sequencing for ion channel gene mutations)

IT Calcium channel
Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(screening for genetic disease involving; single-strand conformational polymorphism anal. (**SSCP**) and sequencing for ion channel gene mutations)

IT Human
SSCP (single-strand conformation polymorphism)
(single-strand conformational polymorphism anal. (**SSCP**) and sequencing for ion channel gene mutations)

L12 ANSWER 6 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB A pharmaceutical analgesic compn. comprising an opioid analgesic agent and a compd. that binds to the **SS1** or **SS2 subunit** of a **sodium channel**, such as tetrodotoxin and saxitoxin, and analogs thereof. Administration of an opioid analgesic agent and a compd. that binds to the **SS1** or **SS2 subunit** of a **sodium channel**, such as tetrodotoxin and saxitoxin, and their analogs, produces analgesia in the treatment of pain in mammals. For example, the synergistic analgesia effect produced by co-administering tetrodotoxin (TTX) and morphine was obsd. in a formalin test in rats. Morphine used alone at 0.30 mg/kg only produced 10.2% inhibition of formalin-induced pain. Combination of TTX at 0.19 .mu.g/kg with morphine at 2.50 mg/kg increased the inhibition rate to 86.7% from 34.9% where the latter was used alone. TTX at a dose of 0.39 .mu.g/kg (1/50 of LD50) produced an inhibition rate of 32.9% when used alone and 66.2% in combination with 0.15 mg/kg of morphine, whereas the latter only produced an inhibition rate of 7.2% when used alone.

IT **Sodium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**SS1** or **SS2 subunit**; synergistic analgesic activity of combination of opioid and **sodium channel** blocker)

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002094272	A1	20021128	WO 2002-CN339	20020520

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	CN 1386505	A	20021225	CN 2001-118098	20010518
	US 2002198226	A1	20021226	US 2002-62483	20020205

L12 ANSWER 7 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Genetic polymorphisms in the beta-**subunit** of the epithelial **sodium channel** (.beta.ENaC) gene in the Japanese population

AB Mutations have been found only in exons 8 and 12 of the .beta.-**subunit** of the epithelial **sodium channel** (.beta.ENaC), but the presence of other mutations in the remaining exons remains to be detd. in the Japanese population. New cases with the V434M mutation should be identified because the identified individuals have high plasma sodium concn. Exons 1 to 7 and 9 to 11 were screened by using single-strand conformational polymorphism (**SSCP**) in 200 subjects (100 normotensive and 100 hypertensive) randomly selected from 1245

participants in a community-based cohort study (Ohasama study) in northern Japan. Four novel mutations were detected in exons 5, 6, and 7, and one of them was the novel missense mutation, P369H in exon 6. Then extended investigation of this mutation, together with those of V434M and P592S, which were identified in our previous studies, was performed in 1245 subjects. The final frequency of these mutations was 1/1245 for P369H, 5/1245 for V434M, and 5/1245 for P592S. Although a significant assocn. with hypertension was not achieved, 3 of the 5 subjects with V434M were diagnosed as hypertensive. Plasma sodium concns. were significantly high and plasma renin activity tended to be low in subjects with V434M. The only subject with P369H showed slightly elevated diastolic pressure, but no other abnormal characteristics were noted in the subjects with P369H or P592S. Genetic polymorphisms of .beta.ENaC in the Japanese population were detd. Clin. features in those with the V434M mutation suggest the presence of physiol. effects of this mutation on plasma sodium regulation.

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(beta-**subunit** of epithelial **sodium channel**
; genetic polymorphisms in beta-**subunit** of epithelial
sodium channel gene in Japanese population with and
without hypertension)

IT Genetic element
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(exon, 5, 6, 7 of .beta.ENaC gene; genetic polymorphisms in beta-
subunit of epithelial **sodium channel** gene
in Japanese population with and without hypertension)

IT Genetic polymorphism
Population genetics
(genetic polymorphisms in beta-**subunit** of epithelial
sodium channel gene in Japanese population)

IT Blood plasma
Genotypes
Human
Human groups
Hypertension
(genetic polymorphisms in beta-**subunit** of epithelial
sodium channel gene in Japanese population with and
without hypertension)

IT Mutation
(missense; genetic polymorphisms in beta-**subunit** of
epithelial **sodium channel** gene in Japanese
population with and without hypertension)

IT Mutation
(silent; genetic polymorphisms in beta-**subunit** of epithelial
sodium channel gene in Japanese population with and
without hypertension)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(.beta.ENaC; genetic polymorphisms in beta-**subunit** of
epithelial **sodium channel** gene in Japanese
population with and without hypertension)

IT 7440-23-5, Sodium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(genetic polymorphisms in beta-**subunit** of epithelial
sodium channel gene in Japanese population with and
without hypertension)

L12 ANSWER 8 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB The compn. of the present invention comprises a sodium channel blocking compd. which is capable of specifically binding to a site, either on an **SS1** region or an **SS2** region, on an extracellular region

of a **sodium channel** alpha **subunit**, and a pharmaceutically acceptable carrier. An injection contained tetrodotoxin 1.5, 0.5% acetic acid 0.1, propylene glycol 80, and water for injection 100 mL. Stability of tetrodotoxin against light, heat, and storage time was studied.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002041915	A1	20020530	WO 2001-CN1566	20011119

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1353990	A	20020619	CN 2000-132672	20001122
US 2002119987	A1	20020829	US 2001-819796	20010329
US 6559154	B2	20030506		
AU 2002021491	A5	20020603	AU 2002-21491	20011119

L12 ANSWER 9 OF 67 CAPLUS

AB Brugada syndrome is characterized by a marked ST-segment elevation in the right precordial leads and is assocd. with a high risk for sudden death. Some reports have indicated SCN5A gene as the candidate gene causing Brugada syndrome. We analyzed not only arrhythmic events but also SCN5A gene mutations in 40 patients with Brugada syndrome to evaluate the genotype-phenotype correlations. Seven patients (17%) experienced ventricular fibrillation or syncope (aborted SCD) and the other 33 patients had no aborted SCD. Paroxysmal atrial fibrillation was present in 10 of the 40 patients (25%) and events of aborted SCD and/or paroxysmal atrial fibrillation occurred in 17 patients (42%). Arrhythmic events, that were aborted SCD or paroxysmal atrial fibrillation, occurred frequently at night and the ST-segment was elevated more prominently when arrhythmic events occurred. In SCN5A gene anal. of all patients by PCR-**SSCP** and direct sequence methods, 4 novel sequence variations leading to amino acid replacement (R282H, H568R, P1090L, and R1193Q) were identified in the patients. A 51 yr-old man with a R282H mutation in the S5-pore lesion had ventricular fibrillation at night and had a elder brother with sudden death at 32 yr of age. This patient had circadian the ST-segment variations, and autonomic nervous drugs could change the degree and the form of ST-segment elevation. R282H mutation was not detected in any of 100 normal control subjects. However H568R, P1090L, and R1193Q mutations in linkers of domain I-II or domain II-III were also found in the normal control subjects (9%, 2%, 6%, resp.). Brugada syndrome seems to be related not only to aborted SCD but also to paroxysmal atrial fibrillation, and may be related to pronounced ST-segment elevation. And the SCN5A gene mutation in the S5-pore region could be the cause of typical Brugada syndrome. ST-segment elevation in patients with this mutation may be influenced by the autonomic nervous function.

IT Genotypes
Human
Phenotypes
SSCP (single-strand conformation polymorphism)
Susceptibility (genetic)
(SCN5A gene mutations in humans with Brugada syndrome with respect to genotype-phenotype correlations)

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(gene SCN5A .alpha.-**subunit**; SCN5A gene mutations in humans with Brugada syndrome with respect to genotype-phenotype correlations)

L12 ANSWER 10 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB The gene for the .beta.-**subunit** of the epithelial **sodium channel** (.beta.ENaC) is one of the most prominent candidate genes being analyzed for an assocn. with human essential hypertension. It is known that a deletion or alteration of PY motif in exon 12 of .beta.ENaC is responsible for Liddle's syndrome. Although the localization of genetic polymorphisms of .beta.ENaC is unique to each population, intensive anal. of individuals of white and African ancestry has demonstrated that genetic variants are localized in exons 8 and 12, with two frequent polymorphisms, G442V in exon 8 and T594M in exon 12. These two mutations are both found in individuals of African ancestry, and might be assocd. with elevated blood pressure (BP). Previously, the authors have screened the last two-thirds of exon 12 in the Japanese population, and demonstrated the absence of the T594M mutation and the presence of a novel P592S mutation. In the present study, the authors further examd. the rest of exon 12 and exon 8 in a general population from Ohasama, Japan (the Ohasama Study), using single-strand conformational polymorphism (**SSCP**) anal. The authors screened 803 subjects randomly selected from the representative participants, who measured their home and casual BP. The PCR products presenting a shift in **SSCP** gels, as well as controls, were directly sequenced by automated analyzer to identify the mutation. A novel gel shift was noted in exon 12 and sequencing identified a polymorphism at codon Ser 520, leading to no change in amino acid sequence (G77576C TCG.fwdarw.TCC). In exon 8, all three **SSCP** variants were heterogeneous for V434M (GTG.fwdarw.ATG), which is coincident with a rare polymorphism in whites. The G442V mutation, however, was absent from the Japanese population. A novel mutation of exon 12 was not assocd. with a significant difference in clin. features. These results indicate that Japanese people possess three polymorphisms in exon 12, all of which are unique, and one in exon 8. These genetic variants of .beta.ENaC may not influence the BP level of Japanese people.

IT **Sodium channel**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ENaC, .beta.-**subunit**; genotypes of .beta.ENaC gene have little influence on blood pressure level in Japanese population)

L12 ANSWER 11 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB The present invention is concerned with mutations in proteins having biol. functions as ion channels and, more particularly, with such mutations where they are assocd. with idiopathic generalized epilepsies (IGE). The invention relates to mutations identified in **sodium channel**, potassium **channel**, .gamma.-aminobutyric acid receptor and nicotinic acetylcholine receptor **subunit**. A method for identifying the mol. defects responsible for the idiopathic generalized epilepsies (IGE), comprising the steps of: (1) providing sequence information for ion channel subunits; (2) screening a nucleic acid or peptide isolated from a patient affected by an IGE for mol. defects in the ion channel subunits in order to identify two principal defects assocd. with the IGE; and (3) correlating the two principal mol. defects identified with clin. observations in order to establish the combination of mutant subunits involved in the IGE. The invention also relates to agonist, modulator and antagonist of an ion channels subunit and uses in treatment of idiopathic generalized epilepsies.

IT Anticonvulsants
Cell
Drug screening
Genetic linkage
Genetic polymorphism
Genetic vectors
Mutation
SSCP (single-strand conformation polymorphism)
Transformation, genetic
(identification of two principal mutations in ion channels assocd. with

idiopathic generalized epilepsies)

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(.alpha. **subunit** SCN1A; identification of two principal mutations in ion channels assocd. with idiopathic generalized epilepsies)

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(.alpha. **subunit** SCN3A; identification of two principal mutations in ion channels assocd. with idiopathic generalized epilepsies)

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(.alpha. **subunit** SCN8A; identification of two principal mutations in ion channels assocd. with idiopathic generalized epilepsies)

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(.beta.1 **subunit** SCN1B; identification of two principal mutations in ion channels assocd. with idiopathic generalized epilepsies)

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002006521	A1	20020124	WO 2001-AU872	20010718

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L12 ANSWER 12 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Human Voltage-Gated **Sodium Channel** .alpha. **Subunit** Gene, SCN12A

AB CDNAs for splicing variants of a novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, are disclosed. We have cloned a cDNA encoding a novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, from human brain. Two alternative splicing variants for SCN12A have been identified. The longest open reading frame of SCN12A encodes 1791 amino acid residues. The deduced amino acid sequence of SCN12A shows 37-73% similarity with various other mammalian sodium channels. The presence of a serine residue (S360) in the **SS2** segment of domain I suggests that SCN12A is resistant to tetrodotoxin (TTX), as in the cases of rat Scn10a (rPN3/SNS) and rat Scn11a (NaN/SNS2). SCN12A is expressed predominantly in olfactory bulb, hippocampus, cerebellar cortex, spinal cord, spleen, small intestine, and placenta. Although expression level could not be detd., SCN12A is also expressed in dorsal root ganglia (DRG). Both neurons and glial cells express SCN12A. SCN12A maps to human chromosome 3p23-p21.3. These results suggest that SCN12A is a tetrodotoxin-resistant (TTX-R) sodium channel expressed in the central nervous system and nonneural tissues.

ST cDNA sequence human SCN12A **sodium channel**

subunit alpha isoform; human gene SCN12A tissue mRNA expression splicing; chromosome 3 mapping human SCN12A gene

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SCN12A; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Nervous system
(central, expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Brain
(cerebellar cortex, expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Neuroglia
Placenta
Spinal cord
Spleen
(expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Brain
(hippocampus, expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Chromosome
(human 3; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Nerve
(neuron, expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT RNA splicing
(novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT **Sodium channel**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Brain
(olfactory bulb, expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Intestine
(small, expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT Ganglion
(spinal, expression in; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT 376424-69-0
RL: PRP (Properties)
(Unclaimed; human Voltage-Gated **Sodium Channel** .alpha. **Subunit** Gene, SCN12A)

IT 264114-16-1 264114-17-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL

(Biological study)
(amino acid sequence; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT 252993-77-4, GenBank AF109737 252993-81-0, GenBank AF150882
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, cDNA sequence, mRNA splicing, expression, and chromosomal mapping)

IT 217895-20-0, 6: PN: WO0174903 SEQID: 6 unclaimed DNA 376424-67-8 376424-68-9 376424-70-3 376424-71-4 376424-72-5 376424-73-6 376424-74-7 376424-75-8 376424-76-9 376424-77-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; human Voltage-Gated **Sodium Channel** .alpha. **Subunit** Gene, SCN12A)

IT 376390-75-9 376390-77-1 376424-78-1 376630-98-7 376630-99-8 376631-05-9 376631-06-0 376631-07-1
RL: PRP (Properties)
(unclaimed sequence; human Voltage-Gated **Sodium Channel** .alpha. **Subunit** Gene, SCN12A)

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2001327294	A2	20011127	JP 2000-152085	20000523
	WO 2001090355	A1	20011129	WO 2000-JP4629	20000711
	W: CA, US				

L12 ANSWER 13 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB Bi-directional PCR Amplification of Specific Allele (bi-PASA) and Single Stranded Conformational Polymorphism (**SSCP**), have been developed for detection of the L1014F mutation in the voltage-sensitive **sodium channel** a-**subunit** gene of permethrin-resistant Colorado potato beetle, Leptinotasa decemlimeata Say (CPB). Both methods allow the simultaneous detection of resistant/susceptible homozygous and heterozygous alleles. These genotyping techniques should allow the precise monitoring of resistant and susceptible allele frequencies in the field population of CPB. To test this possibility, the L1014F-resistant allele frequencies were detd. and compared with the esfenvalerate (a pyrethroid analog of permethrin) resistance level in field populations of CPB. Bi-PASA was used as the primary method and **SSCP** was used as a secondary validating method. The analyzed resistant allele frequency was highly correlated to the pyrethroid resistant levels. Both methods sepd. susceptible and resistant beetles and the results have been validated by direct sequencing.

L12 ANSWER 14 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Neuronal **sodium-channel** .alpha.1-**subunit** mutations in generalized epilepsy with febrile seizures plus

AB Generalized epilepsy with febrile seizures plus (GEFS+) is a familial epilepsy syndrome characterized by the presence of febrile and afebrile seizures. The first gene, GEFS1, was mapped to chromosome 19q and was identified as the **sodium-channel** .beta.1-**subunit**, SCN1B. A second locus on chromosome 2q, GEFS2, was recently identified as the **sodium-channel** .alpha.1-**subunit**, SCN1A. Single-stranded conformation anal. (**SSCA**) of SCN1A was performed in 53 unrelated index cases to est. the frequency of mutations in patients with GEFS+. No mutations were found in 17 isolated cases of GEFS+. Three novel SCN1A mutations-D188V, V1353L, and I1656M-were found in 36 familial cases; of the remaining 33 families, 3 had mutations in SCN1B. On the basis of **SSCA**, the combined frequency of SCN1A and SCN1B mutations in familial cases of GEFS+ was found to be 17%.

IT Gene, animal

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SCN1A; neuronal **sodium-channel** .alpha.1-
subunit mutations in generalized epilepsy with febrile seizures
plus)

IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(exon; neuronal **sodium-channel** .alpha.1-
subunit mutations in generalized epilepsy with febrile seizures
plus)

IT Epilepsy
(generalized epilepsy with febrile seizures plus; neuronal
sodium-channel .alpha.1-**subunit** mutations
in generalized epilepsy with febrile seizures plus)

IT Nerve
(neuron; neuronal **sodium-channel** .alpha.1-
subunit mutations in generalized epilepsy with febrile seizures
plus)

IT Genetic polymorphism
Human
Mutation
(neuronal **sodium-channel** .alpha.1-**subunit**
mutations in generalized epilepsy with febrile seizures plus)

IT **Sodium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neuronal **sodium-channel** .alpha.1-**subunit**
mutations in generalized epilepsy with febrile seizures plus)

L12 ANSWER 15 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI T594M and G442V polymorphisms of the **sodium channel**
.beta. **subunit** and hypertension in a black population

AB Polymorphisms of the epithelial sodium channel may raise blood pressure by increasing renal sodium reabsorption. This study examines frequency distributions and assocns. with hypertension of the T594M and of the G442V polymorphisms of the .beta. **subunit** of the epithelial **sodium channel** in a population-based sample. The authors studied a stratified random sample of 459 subjects (279 women), aged 40-59 yr, of black African origin from general practices' lists within a defined area of South London. All were first generation immigrants. The polymorphic variants were detected using single strand conformational polymorphism technique (**SSCP**). The prevalence of hypertension (BP .gtoreq. 160 and/or 95 mm Hg or on drug therapy) was 43%; of these, 76% were on drug therapy. The main anal. was carried out by three ordered blood pressure categories (I to III) according to increasing blood pressure and presence or absence of drug therapy. The frequency of the 594M variant (heterozygotes and homozygotes) was 4.6%; the frequency of the 442V variant was higher (27.0%). The frequency of the 594M variant increased with increasing blood pressure category (P = 0.05) and was more common in hypertensives than normotensives. By contrast the frequency of the 442V variant did not vary across increasing blood pressure categories (P = 0.62). No gender difference was obsd. Adjustment for age, sex and body mass index did not alter these findings. These results suggest that the 594M variant may contribute to high blood pressure in black people of African origin whereas the G442V polymorphism is unlikely to influence blood pressure in this population.

IT Allele frequency
Genetic polymorphism
Human
Human groups
Hypertension
Mutation
(T594M and G442V polymorphisms of **sodium channel**
.beta. **subunit** and hypertension in black population)

IT **Sodium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(T594M and G442V polymorphisms of **sodium channel** .beta. **subunit** and hypertension in black population)

L12 ANSWER 16 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

IT Peptide receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**SSR** (signal peptide sequence receptor), .gamma. subunit, gene encoding; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

IT **Sodium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(voltage-dependent, .beta.1 **subunit**, gene encoding; methods for treatment of human Huntington's disease and drug screening in relation to gene expression related to signaling modulated by mutant huntington protein)

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034633	A2	20010517	WO 2000-US30900	20001110
	WO 2001034633	A3	20020110		

W: AU, CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 2001017602	A5	20010606	AU 2001-17602	20001110

L12 ANSWER 17 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB Long-QT syndrome (LQTS) is a cardiovascular disorder characterized by a prolonged QT interval on the surface ECG and causes syncope and sudden death as a result of torsade de pointes and ventricular fibrillation. Two major clin. syndromes have been characterized based on the pattern of transmission of the disease: a more common autosomal dominant form with a pure cardiac phenotype (Romano-Ward) and a rare autosomal recessive form characterized by the coexistence of cardiac abnormalities and congenital deafness (Jervell and Lange-Nielsen). Five disease genes have been identified. KVLQT1, HERG, KCNE1, and KCNE2 encode potassium channel **subunits**, and SCN5A encodes the cardiac **sodium channel**. In this study, we described two missense mutations of the HERG channel found in Japanese families affected by long-QT syndrome and characterized the electrophysiol. properties of these mutations using the heterologous expression system in Xenopus oocytes. Regions encoding membrane-spanning domains and the pore domain of the HERG gene were amplified by PCR, and variant conformers were detected by PCR-single strand conformational polymorphism (PCR-**SSCP**). Subsequent direct sequencing of the PCR products confirmed their mutations. The mutations were confined by PCR-restriction fragment length polymorphism (PCR-RFLP). Site-directed mutagenesis was performed, and cRNAs were synthesized. Membrane currents were recorded from oocytes injected with cRNAs by the two-microelectrode voltage-clamp technique. Two missense mutations in the HERG gene were identified from two probands with LQTS. The first mutation was a C-to-T transition in the S4 region of HERG, resulting in amino acid substitution of Arg to Cys at the codon 534 (Arg534Cys). This mutation was identified in three individuals of the family. Three individuals had a prolonged QTc interval, and in them a diagnosis of LQTS was confirmed based on the LQTS criteria. In the electrophysiol. study, quant. analyses revealed that the R534C mutation did not cause apparent dominant-neg. suppression, while kinetic analyses revealed that this mutation shifted the voltage-dependence of HERG channel activation to a neg. direction and accelerated the deactivation time course. The second mutation was a G-to-A transversion in the S5-S6 linker of HERG. resulting in amino acid substitution of Glu to Lys at the codon 637 (Glu637Lys). This was a novel mutation. This mutation was identified in three individuals of the family. Three individuals had a prolonged QTc

interval, and in them a diagnosis of LQTS was confirmed based on the LQTS criteria. The electrophysiol. study revealed that the E637K mutation caused a marked redn. of Ir via a dominant neg. effect.

L12 ANSWER 18 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Study of the voltage-gated **sodium channel** .beta.1 **subunit** gene (SCN1B) in the benign familial infantile convulsions syndrome (BFIC)

AB Benign familial infantile convulsions (BFIC) is a rare autosomal dominant epilepsy syndrome. This syndrome has been recently described in Italian and French pedigrees. Patients present with partial, then generalized seizures, with onset at age three months. The seizures usually spontaneously cease after one year without treatment, leaving no neurol. abnormalities. We have mapped BFIC to chromosome 19q in five Italian pedigrees. The **sodium channel** .beta.1 **subunit** gene (SCN1B) maps to this candidate region and has been shown to be involved in one Australian pedigree with generalized epilepsy and febrile seizures "plus" (GEFS +). In this family, a missense mutation in SCN1B cosegregates with the GEFS+ phenotype. BFIC and GEFS+ have clin. features in common, therefore SCN1B is a candidate gene for BFIC. We studied SCN1B exons 1, 2, 3, 4, and 5, using four **SSCP** methods in 10 Caucasian BFIC probands of Western Europe. We found no exon variants. One variant was identified in intron 5 (IVS5-10C>G), which did not segregate with BFIC and was obsd. in 9.2% controls. A second variant in intron 5 was identified (IVS5+30G>A). It was rare, as not obsd. in controls, but not segregating with the BFIC phenotype.

IT **Sodium channel**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(.beta.1-**subunit**; SCN1B gene mutation in benign familial infantile convulsions syndrome in human Europian population)

L12 ANSWER 19 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Japanese individuals do not harbor the T594M mutation but do have the P592S mutation in the C-terminus of the .beta.-**subunit** of the epithelial **sodium channel**: The Ohasama Study

AB Objective: To assess the implications of polymorphisms of the amiloride-sensitive epithelial sodium channel in essential hypertension in the Japanese population by detg. the incidence of the T594M mutation in the .beta. **subunit** of the epithelial **sodium channel**, and by screening the C-terminus of the epithelial sodium channel. Methods: Single-strand confirmational polymorphism (**SSCP**) anal. using two sets of primers which cover the last two-thirds of the last exon coding the B epithelial sodium channel and modification of a specific enzyme restriction site (NlaIII) for the T594M mutation were performed on 803 Japanese subjects. They were randomly selected from the study participants representative of a general population of Ohasama, Japan, who measured their home blood pressure. Polymerase chain reaction (PCR) products presenting a shift in **SSCP** gel, as well as controls, were directly sequenced by automated analyzer to identify the mutation. **SSCP** anal. identified altered migration in five subjects. Four **SSCP** variants found by sequencing were heterogeneous for the P592S (CCT to TCT) mutation conserving the PY motif, although it was not significantly assocd. with either home or casual blood pressure values. The resting polymorphism was at codon Thr 594, leading to no change in the amino acid sequence (ACG to ACA). None of the PCR products were modified by NlaIII, indicating the absence of the T594M mutation. The epithelial sodium channel variants at the C-terminus are not involved in the common form of essential hypertension in Japanese.

IT Genetic polymorphism
Population genetics
(Japanese individuals do not harbor T594M mutation but do have the P592S mutation in C-terminus of .beta.-**subunit** of epithelial **sodium channel**)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(epithelial sodium channel-encoding; Japanese individuals do not harbor T594M mutation but do have the P592S mutation in C-terminus of .beta.-**subunit** of epithelial **sodium channel**)

IT Mutation
(substitution; Japanese individuals do not harbor T594M mutation but do have the P592S mutation in C-terminus of .beta.-**subunit** of epithelial **sodium channel**)

IT **Sodium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-**subunit**; Japanese individuals do not harbor T594M mutation but do have the P592S mutation in C-terminus of .beta.-**subunit** of epithelial **sodium channel**)

L12 ANSWER 20 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB Resistance to insecticides is a worldwide problem that is increasing in scope and intensity. One means to address this problem is resistance management based on the genetics, biochem. and mol. biol. of the pest organism and the operational factors involved in control. We study the Colorado potato beetle (CPB), a major pest with substantial resistance problems, to investigate the mol. mechanisms of resistance and as a model system to evaluate the effectiveness of operational aspects of control. Using a homol. probing strategy, we have PCR amplified cDNA and genomic DNA fragments that contain point mutation sites assocd. with target site insensitivity to OP/carbamate and DDT/pyrethroid insecticides. Specifically, the S291G mutation within the acetylcholinesterase gene is assocd. with azinphosmethyl and carbofuran insensitivity and resistance and the L757F mutation, which corresponds to the kdr house fly L1014F mutation, within the **sodium channel** a-**subunit** gene is assocd. with DDT and permethrin nerve insensitivity and knockdown-type resistance. To efficiently validate the mutation detection process and to base the DNA diagnostic method on direct sequence information, a single-stranded conformational polymorphism (**SSCP**) protocol and a minisequencing reaction have been coupled. This strategy is easy, rapid, cheap and rugged and applicable for the detection of most point mutations in any resistant strain of insect for monitoring.

L12 ANSWER 21 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Identification of a Novel Human Voltage-Gated **Sodium Channel** .alpha. **Subunit** Gene, SCN12A

AB We have cloned a cDNA encoding a novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A, from human brain. Two alternative splicing variants for SCN12A have been identified. The longest open reading frame of SCN12A encodes 1791 amino acid residues. The deduced amino acid sequence of SCN12A shows 37-73% similarity with various other mammalian sodium channels. The presence of a serine residue (S360) in the **SS2** segment of domain I suggests that SCN12A is resistant to tetrodotoxin (TTX), as in the cases of rat Scn10a (rPN3/SNS) and rat Scn11a (NaN/SNS2). SCN12A is expressed predominantly in olfactory bulb, hippocampus, cerebellar cortex, spinal cord, spleen, small intestine, and placenta. Although expression level could not be detd., SCN12A is also expressed in dorsal root ganglia (DRG). Both neurons and glial cells express SCN12A. SCN12A maps to human chromosome 3p23-p21.3. These results suggest that SCN12A is a tetrodotoxin-resistant (TTX-R) sodium channel expressed in the central nervous system and nonneural tissues. (c) 2000 Academic Press.

ST cDNA sequence human SCN12A **sodium channel subunit** alpha isoform; human gene SCN12A tissue mRNA expression splicing; chromosome 3 mapping human SCN12A gene

IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC

(Process)
(SCN12A; identification, cDNA sequence, mRNA splicing and expression, and chromosomal mapping of novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A)

IT **Sodium channel**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(gene SCN12A isoforms, voltage-gated, .alpha. **subunit**; identification, cDNA sequence, mRNA splicing and expression, and chromosomal mapping of novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A)

IT Chromosome
(human 3; identification, cDNA sequence, mRNA splicing and expression, and chromosomal mapping of novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A)

IT Genetic mapping
Protein sequences
RNA splicing
cDNA sequences
(identification, cDNA sequence, mRNA splicing and expression, and chromosomal mapping of novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A)

IT mRNA
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(identification, cDNA sequence, mRNA splicing and expression, and chromosomal mapping of novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A)

IT 264114-16-1 264114-17-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; identification, cDNA sequence, mRNA splicing and expression, and chromosomal mapping of novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A)

IT 252993-77-4, GenBank AF109737 252993-81-0, GenBank AF150882
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; identification, cDNA sequence, mRNA splicing and expression, and chromosomal mapping of novel human voltage-gated **sodium channel** .alpha. **subunit** gene, SCN12A)

L12 ANSWER 22 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Functional roles of the extracellular segments of the **sodium channel** .alpha. **subunit** in voltage-dependent gating and modulation by .beta.1 subunits

AB Voltage-gated **sodium channels** consist of a pore-forming .alpha. **subunit** assocd. with .beta.1 **subunits** and, for brain **sodium channels**, .beta.2 **subunits**. Although much is known about the structure and function of the .alpha. subunit, there is little information on the functional role of the 16 extracellular loops. To search for potential functional activities of these extracellular segments, chimeras were studied in which an individual extracellular loop of the rat heart (rH1) .alpha. subunit was substituted for the corresponding segment of the rat brain type IIA (rIIA) .alpha. subunit. In comparison with rH1, wild-type rIIA .alpha. subunits are characterized by more pos. voltage-dependent activation and inactivation, a more prominent slow gating mode, and a more substantial shift to the fast gating mode upon coexpression of .beta.1 subunits in Xenopus oocytes. When .alpha. subunits were expressed alone, chimeras with substitutions from rH1 in five extracellular loops (IIS5-**SS1**, IISS2-S6, IIIS1-S2, IIISS2-S6, and IVS3-S4) had neg. shifted

activation, and chimeras with substitutions in three of these (IISS2-S6, IIIS1-S2, and IVS3-S4) also had neg. shifted steady-state inactivation. RIIA .alpha. subunit chimeras with substitutions from rH1 in five extracellular loops (IS5-**SS1**, ISS2-S6, IISS2-S6, IIIS1-S2, and IVS3-S4) favored the fast gating mode. Like wild-type rIIA .alpha. subunits, all of the chimeric rIIA .alpha. subunits except chimera IVSS2-S6 were shifted almost entirely to the fast gating mode when coexpressed with .beta.1 subunits. In contrast, substitution of extracellular loop IVSS2-S6 substantially reduced the effectiveness of .beta.1 subunits in shifting rIIA .alpha. subunits to the fast gating mode. Our results show that multiple extracellular loops influence voltage-dependent activation and inactivation and gating mode of sodium channels, whereas segment IVSS2-S6 plays a dominant role in modulation of gating by .beta.1 subunits. Evidently, several extracellular loops are important determinants of sodium channel gating and modulation.

IT Electric current
(biol., gating; functional roles of extracellular segments of **sodium channel** .alpha. **subunit** in voltage-dependent gating and modulation by .beta.1 subunits)

IT Biological transport
(sodium; functional roles of extracellular segments of **sodium channel** .alpha. **subunit** in voltage-dependent gating and modulation by .beta.1 subunits)

IT **Sodium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(voltage-gated, .alpha. and .beta. **subunits**; functional roles of extracellular segments of **sodium channel** .alpha. **subunit** in voltage-dependent gating and modulation by .beta.1 subunits)

IT Fusion proteins (chimeric proteins)
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(.alpha. **subunits** of heart and brain **sodium channels**; functional roles of extracellular segments of **sodium channel** .alpha. **subunit** in voltage-dependent gating and modulation by .beta.1 subunits)

IT 7440-23-5, Sodium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; functional roles of extracellular segments of **sodium channel** .alpha. **subunit** in voltage-dependent gating and modulation by .beta.1 subunits)

L12 ANSWER 23 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Study on amiloride sensitive **sodium channel** .beta. **subunit** exon 12 gene mutation by PCR-**SSCP** in primary hypertension

AB The exon 12 of amiloride sensitive **sodium channel** (ASSC) .beta. **subunit** gene mutation in patients with primary hypertension was studied in 148 definite primary hypertension subjects, PCR-**SSCP** was used to screen and define the mutation. PCR-**SSCP** detected changes of ASSC .beta. subunit gene exon 12 in 3 cases. The mutation of ASSC .beta. subunit gene exon 12 might be related to primary hypertension, and this gene mutation might be one of the mol. mechanism for some common forms of patients with primary hypertension.

IT Hypertension
(essential; study on amiloride sensitive **sodium channel** .beta. **subunit** exon 12 gene mutation by PCR-**SSCP** in primary hypertension)

IT Mutation
(study on amiloride sensitive **sodium channel** .beta. **subunit** exon 12 gene mutation by PCR-**SSCP** in primary hypertension)

IT Gene, animal
Sodium channel
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(study on amiloride sensitive **sodium channel** .beta.
subunit exon 12 gene mutation by PCR-**SSCP** in primary
hypertension)
IT 2609-46-3, Amiloride
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(study on amiloride sensitive **sodium channel** .beta.
subunit exon 12 gene mutation by PCR-**SSCP** in primary
hypertension)

L12 ANSWER 24 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
TI Voltage-gated **sodium channel** .alpha.-**subunit**
expressed in dorsal root ganglia and trigeminal ganglia
AB A novel Na channel .alpha.-subunit (NaN), predicted to be TTX-R and voltage-gated, is provided that is expressed preferentially in sensory neurons within dorsal root ganglia (DRG) and trigeminal ganglia. The predicted amino acid sequence of NaN can be aligned with the predicted structure of known Na channel .alpha.-subunits; all relevant landmark sequences, including pos. charged S4 and pore-lining **SS1-SS2** segments, and the inactivation tripeptide IFM, are present at predicted positions. However, NaN exhibits only 42-53% similarity to other mammalian Na channels, including SNS/PN3, indicating that it is a novel channel, and suggesting that it may represent a third subfamily of Na channels. NaN transcript levels are reduced significantly 7 days post axotomy in DRG neurons, consistent with previous findings of a redn. in TTX-R Na currents. The preferential expression of NaN in DRG and trigeminal ganglia and the redn. of NaN mRNA levels in DRG after axonal injury suggest that NaN, together with SNS/PN3, may produce TTX-R currents in peripheral sensory neurons and may influence the generation of elec. activity in these cells. Nucleotide cDNA and deduced protein sequences are also provided for mouse and partial human NaN homologs, and a alternative splicing variant of rat NaN, as well as microsatellite DNA sequences present in the introns of the mouse gene. The preferential expression of NaN on sensory, but not other neurons, makes it a very useful target for diagnostic and/or therapeutic uses in relation to acute and/or chronic pain pathologies, paraesthesia, and/or hyperexcitability.
IT Gene, animal
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);
BIOL (Biological study); OCCU (Occurrence)
(Scn11a, mouse gene location on chromosome 9; voltage-gated
sodium channel .alpha.-**subunit** expressed in
dorsal root ganglia and trigeminal ganglia)
IT Nerve
(axotomy; voltage-gated **sodium channel** .alpha.-
subunit expressed in dorsal root ganglia and trigeminal
ganglia)
IT Membrane potential
(biol., for screening modulators and detection of **sodium
channel**; voltage-gated **sodium channel**
.alpha.-**subunit** expressed in dorsal root ganglia and
trigeminal ganglia)
IT Nervous system
(disease, hyperexcitability, treatment of; voltage-gated **sodium
channel** .alpha.-**subunit** expressed in dorsal root
ganglia and trigeminal ganglia)
IT Molecular cloning
(expression system; voltage-gated **sodium channel**
.alpha.-**subunit** expressed in dorsal root ganglia and
trigeminal ganglia)
IT Scintigraphy
(for screening modulators and detection of **sodium
channel**; voltage-gated **sodium channel**

.alpha.-**subunit** expressed in dorsal root ganglia and
trigeminal ganglia)

IT Genetic mapping
(gene location on mouse chromosome 9; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Nucleic acid hybridization
(in situ, for screening modulators and detection of **sodium channel**; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Antibodies
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(monoclonal; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Chromosome
(mouse 9, gene location on mouse chromosome 9; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT DNA sequences
(of intronic microsatellites in voltage-gated **sodium channel** .alpha.-**subunit** gene from mouse)

IT Protein sequences
(of voltage-gated **sodium channel** .alpha.-**subunit** from mouse and rat and human)

IT Tooth
(paresthesia, treatment of; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Nerve
(peripheral, sensory; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Mutation
(screening for mutant alleles using intronic microsatellite sequences; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Microsatellite DNA
RL: ARG (Analytical reagent use); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(screening for mutant alleles using intronic microsatellite sequences; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Ganglion
(spinal; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Pain
(treatment of; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Ganglion
(trigeminal; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT Drug screening
Gene therapy
Mouse
Rat
(voltage-gated **sodium channel** .alpha.-

subunit expressed in dorsal root ganglia and trigeminal ganglia)

IT Antibodies
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT **Sodium channel**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(.alpha.-**subunit** NaN; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT 212255-48-6 234087-98-0 235091-90-4 235091-93-7
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT 7440-23-5, Sodium, biological studies 13966-32-0, Sodium-22, biological studies 14932-53-7, Rubidium-86, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(influx, for screening modulators and detection of **sodium channel**; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT 235091-94-8 235091-95-9 235091-96-0 235091-97-1 235091-98-2 235091-99-3 235092-00-9 235092-01-0 235092-02-1
RL: ARU (Analytical role, unclassified); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence)
(nucleotide sequence; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT 235091-89-1 235091-92-6
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

IT 211882-55-2, Genbank AF059030
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; voltage-gated **sodium channel** .alpha.-**subunit** expressed in dorsal root ganglia and trigeminal ganglia)

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9938889	A2	19990805	WO 1999-US2008	19990129
	W: AU, CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2319143	AA	19990805	CA 1999-2319143	19990129
	AU 9924856	A1	19990816	AU 1999-24856	19990129
	EP 1053250	A1	20001122	EP 1999-904457	19990129
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002509860	T2	20020402	JP 2000-529355	19990129
	US 6573067	B1	20030603	US 1999-354147	19990716

L12 ANSWER 25 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Two novel mutations in the .beta. **subunit** of the human epithelial **sodium channel**

AB Liddle syndrome is characterized by severe hypertension, hypokalemia, suppressed plasma renin activity, and low aldosterone levels. Genetic defects in the .beta. **subunit** of the human epithelial **sodium channel** (h.beta.ENaC) been identified in patients with Liddle syndrome,. By **SSCP** anal., the authors identify two hemodialysis patients of Eastern European origin with novel heterozygous mutations in the human epithelial **sodium channel** .beta. **subunit** that have been verified by direct nucleotide sequence anal. These mutations were located at codon 567 (1700 C.fwdarw.T) and codon 592 (1776 G.fwdarw.A), leading to a an Ala.fwdarw.Val substitution at 567 whereas the threonine at codon 592 remained unchanged. Family members of the patients were not available for genetic testing. The authors data show that there is genetic heterogeneity in h.beta.ENaC in Europe. The Ala567Val exchange may contribute to the development of renal failure and progression to end-stage renal disease by aggravation of hypertension.

ST **sodium channel** mutation beta **subunit** hemodialysis kidney failure

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(epithelial, .beta.-**subunit**; mutations in .beta. **subunit** of epithelial **sodium channel** in humans with renal failure on hemodialysis)

IT Kidney, disease
(failure; mutations in .beta. **subunit** of epithelial **sodium channel** in humans with renal failure on hemodialysis)

IT Dialysis
(hemodialysis; mutations in .beta. **subunit** of epithelial **sodium channel** in humans with renal failure on hemodialysis)

IT Mutation
(in .beta. **subunit** of epithelial **sodium channel** in humans with renal failure on hemodialysis)

IT Hypertension
(mutations in .beta. **subunit** of epithelial **sodium channel** in humans with renal failure on hemodialysis)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(mutations in .beta. **subunit** of epithelial **sodium channel** in humans with renal failure on hemodialysis)

IT Aldosteronism
(pseudoaldosteronism; mutations in .beta. **subunit** of epithelial **sodium channel** in humans with renal failure on hemodialysis in relation to)

L12 ANSWER 26 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB The .gamma. subunit of the epithelial Na channel (.gamma.ENaC) has been implicated in Liddle's syndrome. The objective of this study was to examine its status in essential hypertension. The search for mol. variants was performed using the **SSCP** technique after detn. of the intron-exon boundaries of the transcribed sequence. We found an addnl. 205 bp intron splitting the published exon 10 in two. The last exon of .gamma.ENaC was tested with samples from a series of 245 normotensive patients and 453 hypertensive subjects (383 Caucasians, 70 Afro-Caribbeans), all probands of hypertensive families in the HYPERGENE data set. The search was extended to the other 11 transcribed exons in a subset of 65 patients with low-renin profile. Four neutral polymorphisms

were detected, three in the third exon of the gene (T387C, T474C, C549T) and one in the last exon (C1990G). These four variants were found with similar frequencies in hypertensive and normotensive Caucasian subjects as well as in patients with low-renin profile. Hypertensive Caucasians and hypertensive subjects of African ancestry also had similar frequencies. Lastly, we found two rare mutations, one the insertion of a proline residue at position 594 of the mature protein (594insP), the other an Arg-to-His substitution at position 631 (R631H). Compared to wild-type (1.00), expression of the 594insP (1.10) and R631H (0.97) variants in Xenopus oocytes produced no significant increase in Na+ current. Screening of the entire coding sequence of .gamma.ENaC does not suggest that this subunit is frequently involved in essential hypertension.

IT **Sodium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(polymorphisms of .gamma. **subunit** of the epithelial Na+ channel in human essential hypertension)

L12 ANSWER 27 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
TI Molecular analysis of the carboxy terminus of the beta and gamma **subunits** of the epithelial **sodium channel** in patients with end-stage renal disease
IT Allele frequency
Mutation
SSCP (single-strand conformation polymorphism)
(mol. anal. of the carboxy terminus of the .beta. and .gamma. subunits of the epithelial Na channel in end-stage renal disease)

L12 ANSWER 28 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AB Although physiol. and pharmacol. evidence suggests the presence of multiple tetrodotoxin-resistant (TTX-R) Na channels in neurons of peripheral nervous system ganglia, only one, SNS/PN3, has been identified in these cells to date. We have identified and sequenced a novel Na channel .alpha.-subunit (NaN), predicted to be TTX-R and voltage-gated, that is expressed preferentially in sensory neurons within dorsal root ganglia (DRG) and trigeminal ganglia. The predicted amino acid sequence of NaN can be aligned with the predicted structure of known Na channel .alpha.-subunits; all relevant landmark sequences, including pos. charged S4 and pore-lining **SS1-SS2** segments, and the inactivation tripeptide IFM, are present at predicted positions. However, NaN exhibits only 42-53% similarity to other mammalian Na channels, including SNS/PN3, indicating that it is a novel channel, and suggesting that it may represent a third subfamily of Na channels. NaN transcript levels are reduced significantly 7 days post axotomy in DRG neurons, consistent with previous findings of a redn. in TTX-R Na currents. The preferential expression of NaN in DRG and trigeminal ganglia and the redn. of NaN mRNA levels in DRG after axonal injury suggest that NaN, together with SNS/PN3, may produce TTX-R currents in peripheral sensory neurons and may influence the generation of elec. activity in these cells.

IT **Sodium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(.alpha.-**subunit** NaN; voltage-gated Na channel NaN is expressed preferentially in peripheral sensory neurons and down-regulated after axotomy)

L12 ANSWER 29 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
TI The diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**
AB Hypertension is a common multifactorial disorder assocd. with considerable morbidity and mortality. The kidney plays a major role in the long term regulation of blood pressure. Liddle syndrome (pseudo-hyperaldosteronism) is one of a no. of monogenic disorders of salt and water transport. In a

kindred with at least four affected members suffering from Liddle syndrome, we confirmed by direct DNA sequencing the identity of a novel heterozygous mutation in h.beta.ENaC, the gene encoding the .beta. **subunit** of the amiloride sensitive epithelial **sodium channel** which is expressed in the distal nephron. Single stranded conformational polymorphism anal. showed cosegregation of the mutant allele within the kindred with the Liddle phenotype. An insertion of an addnl. cytosine into a string of six located between codons 593 and 595 results in a sequence frameshift and is predicted to produce a protein truncated by 34 amino acids. The availability of a mol. diagnostic tool has implications for the management of hypertension and genetic counselling in families with Liddle syndrome.

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(amiloride sensitive epithelial **sodium channel**, .beta. **subunit**; diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

IT Genetic inheritance
PCR (polymerase chain reaction)
SSCP (single-strand conformation polymorphism)
(diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

IT Mutation
(frameshift; diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

IT Mutation
(insertion; diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

IT Diagnosis
(mol.; diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

IT Aldosteronism
(pseudoaldosteronism; diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(.beta.ENaC (for .beta. **subunit** of the epithelial **sodium channel**); diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

IT 212063-96-2 212063-97-3
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(PCR primer; diagnosis of Liddle syndrome by identification of a mutation in the .beta. **subunit** of the epithelial **sodium channel**)

L12 ANSWER 30 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB Liddle's syndrome is a rare monogenic form of hypertension caused by truncating or missense mutations in the C termini of the epithelial **sodium channel** .beta.- or .gamma.-**subunits**. These mutations delete or alter a conserved proline-rich amino acid sequence referred to as the PY-motif. We report here a Liddle's syndrome family with a .beta.Arg564X mutation with a premature stop codon deleting the PY-motif of the .beta.-subunit. This family shows marked phenotypic variation in blood pressure, serum potassium levels, and age of onset of hypertension. Given the similarity with primary hypertension, changes in the C termini of the .beta.- or .gamma.-subunits may contribute to the

development of primary hypertension or to hypertension assocd. with diabetic nephropathy. Accordingly, the coding sequences for the cytoplasmic C termini of the .beta.- and .gamma.-subunits were screened for mutations with the use of polymerase chain reaction, single-strand conformation polymorphism, and direct DNA sequencing in 105 subjects with primary hypertension and 70 subjects with diabetic nephropathy. One frequent polymorphism was identified, but its frequency did not differ among subjects with primary hypertension, subjects with diabetic nephropathy, or control subjects. Two of the 175 subjects with primary hypertension or diabetic nephropathy showed variants that were not present in 186 control subjects. None of the variants changed the PY-motif sequence. In conclusion, a .beta.Arg564X mutation is the likely cause of Liddle's syndrome in this Swedish family, but it is unlikely that mutations in the .beta.- and .gamma.-**subunit** genes of the epithelial **sodium channel** play a significant role in the pathogenesis of primary hypertension or diabetic nephropathy.

IT Protein sequences
(amino acid sequence of the C-terminal region of human .beta. and .gamma. **subunits** of epithelial **sodium channel**, location of mutation and polymorphic sites)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(for .beta. and .gamma. **subunits** of epithelial **sodium channel**; mutations and variants of the epithelial **sodium channel** gene in Liddle's syndrome and primary hypertension)

IT Genetic inheritance
Genetic polymorphism
PCR (polymerase chain reaction)
SSCP (single-strand conformation polymorphism)
(mutations and variants of the epithelial sodium channel gene in Liddle's syndrome and primary hypertension)

IT Mutation
(nonsense, .beta. **subunit** Arg564X; mutations and variants of the epithelial **sodium channel** gene in Liddle's syndrome and primary hypertension)

L12 ANSWER 31 OF 67 CAPLUS

AB To investigate whether mutations in the C-terminus of the three **subunits** of the rat epithelial **sodium channel** (.alpha..beta..gamma.-rENaC) contribute to the hypertensive phenotype in five rat models for essential hypertension. The authors sequenced the C-terminal regions of .alpha.-, .beta.- and .gamma.-rENaC genes in five different hypertensive rat strains [spontaneously hypertensive rats (SHR), Dahl salt-sensitive (**SS**/Jr) rats, Milan hypertensive (MHS) rats, Sabra hypertensive (SBH) rats and Lyon hypertensive rats (LHR)] and their normotensive controls [Wistar-Kyoto (WKY) rats, Dahl salt-resistant (SR/Jr) rats, Milan normotensive (MNS) rats, Sabra normotensive (SBN) rats and Lyon normotensive rats (LNR)]. Identified polymorphisms were tested for cosegregation with blood pressure as well as for increased epithelial sodium channel (ENaC) activity. Genomic DNA extd. from hypertensive and normotensive rat strains was amplified by the polymerase chain reaction and polymerase chain reaction fragments were sequenced. Cosegregation anal. was performed to test for correlations between blood pressure and different genotypes. The effects of a polymorphism on ENaC activity were assessed by functional expression in Xenopus laevis oocytes. The chromosomal location of the gene for .gamma.-ENaC was detd. by linkage anal. in an F2 (MHS .times. MNS) population. The authors found no polymorphisms at the C-terminus of .alpha.- and .beta.-rENaC in the five rat models tested. The authors identified two polymorphisms at the C-terminus of the .gamma.-subunit, one leading to an amino acid change. Milan strains (MNS and MHS) were polymorphic for this mutation. By

cosegregation anal. the authors could exclude the possibility that there was a correlation between blood pressure and this polymorphism. Functional expression of the polymorphism caused no increase in ENaC activity assessed by measurement of the amiloride-sensitive sodium current in Xenopus oocytes. The gene for the .gamma.-ENAC was located on rat chromosome 1. No polymorphisms at the C-terminus of the three **subunits** of the epithelial **sodium channel** cosegregating with blood pressure were detected in five different genetic rat models for hypertension. If an altered ENaC activity contributes to the pathogenesis of hypertension in these rats, it must thus arise from mutations in other parts of the protein, from mutations outside the coding region impairing the proper regulation of one of the subunits or from mutations in an ENaC-assocd. protein.

IT Hypertension
(essential; polymorphism of **sodium channel** .gamma. **subunit** C-terminus in rat models for hypertension)

IT Disease models
Genetic polymorphism
Mutation
Phenotypes
Rat
(polymorphism of **sodium channel** .gamma. **subunit** C-terminus in rat models for hypertension)

IT **Sodium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(polymorphism of **sodium channel** .gamma. **subunit** C-terminus in rat models for hypertension)

IT Chromosome
(rat, rat 1; **sodium channel** .gamma. **subunit** of rat localization to chromosome 1)

IT Genetic mapping
(**sodium channel** .gamma. **subunit** of rat localization to chromosome 1)

IT Gene, animal
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**sodium channel** .gamma. **subunit** of rat localization to chromosome 1)

IT 7440-23-5, Sodium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; polymorphism of **sodium channel** .gamma. **subunit** C-terminus in rat models for hypertension)

L12 ANSWER 32 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB Using primers derived from sequences for human or mouse genes Adra2a, Adrb1, Calca, Fgfr2, Il4r, Itgam, Pckb, ScnnIb, and Th (encoding .alpha.2-adrenoceptor, .beta.1-adrenoceptor, .alpha.-calcitonin gene-related peptide, fibroblast growth factor receptor 2, interleukin 4 receptor, integrin .alpha.-M, protein kinase C-.beta., epithelial **sodium channel** .beta. **subunit**, and tyrosine hydroxylase, resp.), simple sequence repeat (**SSR**) markers were selected for rat chromosome (Chr) 1. Eleven **SSR** markers were mapped to rat chromosome 1 analogous to mouse Chr 7, but the same genes have been mapped to human Chr 10, 11, and 16. Sa, a candidate gene for hypertension in rat has been mapped to this area of Chr 1 in rats, but has not been assocd. with hypertension in humans. There is a possibility that a hypertension gene is not located on the area of the rat chromosome homologous to human chromosome 16, but an area homologous to either human chromosome 11 or 10.

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological

study); OCCU (Occurrence)
(epithelial, .beta.-**subunit**, gene ScnnIb, microsatellite marker; comparative mapping of novel simple sequence repeat markers in hypertension-related region on rat chromosome 1)

L12 ANSWER 33 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Identification of amino acid residues in the .alpha., .beta., and .gamma. **subunits** of the epithelial **sodium channel** (ENaC) involved in amiloride block and ion permeation

AB The amiloride-sensitive epithelial Na channel (ENaC) is a heteromultimeric channel made of three .alpha..beta..gamma. subunits. The structures involved in the ion permeation pathway have only been partially identified, and the resp. contributions of each subunit in the formation of the conduction pore has not yet been established. Using a site-directed mutagenesis approach, in a **short segment** preceding the second membrane-spanning domain (the pre-M2 segment) amino acid residues involved in ion permeation and crit. for channel block by amiloride have been identified. Cys substitutions of Gly residues in .beta. and .gamma. subunits at position .beta.G525 and .gamma.G537 increased the apparent inhibitory const. (Ki) for amiloride by > 1,000-fold and decreased channel unitary current without affecting ion selectivity. The corresponding mutation S583 to C in the .alpha. subunit increased amiloride Ki by 20-fold, without changing channel conducting properties. Coexpression of these mutated .alpha..beta..gamma. subunits resulted in a non-conducting channel expressed at the cell surface. Finally, these Cys substitutions increased channel affinity for block by external Zn2+ ions, in particular the .alpha.S583C mutant showing a Ki for Zn2+ of 29 .mu.M. Mutations of residues .alpha.W582L or .beta.G522D also increased amiloride Ki, the later mutation generating a Ca2+ blocking site located 15% within the membrane elec. field. These expts. provide strong evidence that .alpha..beta..gamma. ENaCs are pore-forming subunits involved in ion permeation through the channel. The pre-M2 segment of .alpha..beta..gamma. subunits may form a pore loop structure at the extracellular face of the channel, where amiloride binds within the channel lumen. It is proposed that amiloride interacts with Na+ ions at an external Na+ binding site preventing ion permeation through the channel pore.

IT Epithelium
Permeation
(identification of amino acid residues in the .alpha., .beta., and .gamma. **subunits** of the epithelial **sodium channel** (ENaC) involved in amiloride block and ion permeation)

IT Sodium channel
RL: PRP (Properties)
(identification of amino acid residues in the .alpha., .beta., and .gamma. **subunits** of the epithelial **sodium channel** (ENaC) involved in amiloride block and ion permeation)

IT 2609-46-3, Amiloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(identification of amino acid residues in the .alpha., .beta., and .gamma. **subunits** of the epithelial **sodium channel** (ENaC) involved in amiloride block and ion permeation)

IT 7440-23-5, Sodium, biological studies 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(identification of amino acid residues in the .alpha., .beta., and .gamma. **subunits** of the epithelial **sodium channel** (ENaC) involved in amiloride block and ion permeation)

IT 7440-66-6, Zinc, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of amino acid residues in the .alpha., .beta., and .gamma. **subunits** of the epithelial **sodium**

channel (ENaC) involved in amiloride block and ion permeation)

L12 ANSWER 34 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AB Recombinant brain, skeletal muscle, and heart voltage-gated Na+ channel .alpha. subunits differ in their functional responses to an accessory .beta.1 subunit when coexpressed in Xenopus oocytes. We exploited the distinct .beta.1 subunit responses obsd. for the human heart (hH1) and human skeletal muscle (hSkM1) isoforms to identify determinants of this response. Chimeric .alpha. subunits were constructed by exchanging the S5-S6 interhelical loops of each domain between hH1 and hSkM1 and then examd. for effects on inactivation induced by coexpressed .beta.1 subunit in oocytes. Substitution of single S5-S6 loops in either domain 1 (D1/S5-S6) or domain 4 (D4/S5-S6) of hSkM1 by the corresponding segments of hH1 produced channels that exhibited an attenuated response to coexpressed .beta.1 subunit. Substitutions of both D1/S5-S6 and D4/S5-S6 in hSkM1 by the corresponding loops from hH1 completely abolished the effects of the .beta.1 subunit on inactivation. The reciprocal chimera in which both D1/S5-S6 and D4/S5-S6 from hSkM1 were transplanted into hH1 exhibited significant .beta.1 responsiveness (accelerated inactivation). The region within D4/S5-S6 that conferred .beta.1 responsiveness was detd. to reside primarily within an extracellular loop between the putative pore-forming segment **SS2** and D4/S6. Gating modulation was also demonstrated using a chimeric .beta. subunit consisting of the extracellular domains of .beta.1 and the transmembrane and C-terminal domains of the rat brain .beta.2 subunit. These results suggest that the D1/S5-S6 and D4/S5-S6 loops in the .alpha. subunit and the extracellular domain of the .beta.1 subunit are important determinants of the .beta.1 subunit-induced gating modulation in Na+ channels.
ST **sodium channel** gating **subunit** structure
IT **Sodium channel**
RL: PRP (Properties)
(mol. determinants of .beta.1 **subunit**-induced gating modulation in voltage-dependent Na+ channels)

L12 ANSWER 35 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
IT Gene, animal
RL: ANT (Analyte); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(HERG, long QT syndrome-causing mutant, potassium channel major **subunit**-encoding; heart gene HERG and SCN5A mutants, encoded potassium and **sodium channel** mutants, and oligonucleotide or antibody probes for diagnosing long QT syndrome)
IT Genetic polymorphism
(**SSCP** (single-strand conformation polymorphism), heart gene HERG and SCN5A mutants, encoded potassium and sodium channel mutants, and oligonucleotide or antibody probes for diagnosing long QT syndrome)
IT Ion channel
(potassium, gene HERG, rapidly-activating delayed rectifier **subunit**; heart gene HERG and SCN5A mutants, encoded potassium and **sodium channel** mutants, and oligonucleotide or antibody probes for diagnosing long QT syndrome)

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9628537	A1	19960919	WO 1996-US3186	19960308
	W: CA				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5599673	A	19970204	US 1995-401512	19950309
	CA 2214646	AA	19960919	CA 1996-2214646	19960308
	EP 815197	A1	19980107	EP 1996-911268	19960308
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

L12 ANSWER 36 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AB The single strand conformation polymorphism (**SSCP**) technique was

used to screen genomic DNA of a family with myotonia aggravated by cold, potassium loading and suxamethonium, but without muscle weakness. An aberrant band was found in exon 24 of SCN4A, the gene encoding the adult skeletal muscle **sodium channel** .alpha.-**subunit**
. DNA sequencing led to the detection of a G-to-A transition of cDNA nucleotide 4765 predicting a substitution of methionine for valine at position 1589 of the protein sequence. This amino acid is located within transmembrane segment S6 of channel repeat IV close to the cytoplasmic surface, a region which is supposed to act as acceptor of the inactivation gate of the channel. Four lines of evidence indicate that this mutation causes the disease: (i) the transition was only found for affected family members; (ii) no mutations were found in all other SCN4A exons; (iii) the affected gene region is conserved among various species; and (i.v.) an increase in the no. of non-inactivating sodium channels had been revealed in earlier electrophysiol. studies on an excised muscle specimen from the index patient. In addn., the close-by occurring substitution of valine for methionine at position 1592 known to cause hyperkalemic periodic paralysis was deduced for six families with myotonic, non-dystrophic form of this disease.

IT Gene, animal
RL: BIOL (Biological study)
(SCN4A, for **sodium channel** .alpha.-**subunit** of skeletal muscle, transition mutation in, in myotonia aggravated by cold and potassium, of humans)

IT Temperature effects, biological
(cold, myotonia aggravated by potassium and, skeletal muscle **sodium channel** .alpha.-**subunit** gene SCN4A mutation in, of humans)

IT Muscle, disease
(myotonia, potassium and cold aggravation of, skeletal muscle **sodium channel** .alpha.-**subunit** gene SCN4A mutation causing, in humans)

IT Ion **channel**
(**sodium**, .alpha.-**subunit**, of skeletal muscle, gene SCN4A for, transition mutation in, in myotonia aggravated by cold and potassium, of humans)

IT Mutation
(transition, in skeletal muscle **sodium channel** .alpha.-**subunit** gene SCN4A, in myotonia aggravated by cold and potassium, of humans)

IT 7440-23-5, **Sodium**, biological studies
RL: BIOL (Biological study)
(**channel**, .alpha.-**subunit**, of skeletal muscle, gene SCN4A for, transition mutation in, in myotonia aggravated by cold and potassium, of humans)

IT 7440-09-7, Potassium, biological studies
RL: BIOL (Biological study)
(myotonia aggravated by cold and, skeletal muscle **sodium channel** .alpha.-**subunit** gene SCN4A mutation in, of humans)

L12 ANSWER 37 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB The time course of developmental accumulation of the 9-kilobase mRNA encoding Na+ channel .alpha. subunits (260 kDa) in the rat forebrain was measured by RNA blotting. These transcripts were present at low levels until birth, increased rapidly in abundance to peak by postnatal day 7, and subsequently declined to 50% of this max. value in adult animals. Na+ channel gene transcription measured by a nuclear run-on assay was first detectable on embryonic day 16, increased to a max. on postnatal days 1-7, and declined in adulthood. The level of gene transcription was highest during the period of rapid rise of Na+ channel .alpha. subunit mRNA levels and decreased during the period of Na+ channel mRNA decline. The levels of Na+ channel .alpha. subunit protein measured by immunoblotting increased from postnatal day 1 to postnatal day 21, with the greatest rate

of increase falling between days 7 and 21. The no. of high-affinity saxitoxin-binding sites increased in parallel to the increase in .alpha. subunit protein. The period of the most rapid rise in Na+ channel .alpha. subunit levels corresponded to the period of greatest Na+ channel mRNA abundance. Na+ channel .alpha. subunits were resolved into free .alpha. subunits and .alpha. subunits **SS**-linked to .beta.2 subunits. On postnatal day 1, virtually all Na+ channel .alpha. subunits were in the free .alpha. form. The fraction of **SS**-linked .alpha. subunits increased to 60% by postnatal day 21 and 90% by postnatal day 90. The concn. of free .alpha. subunits was max. on postnatal days 7-14 and declined to <10% in adulthood. Thus, the formation of mature heterotrimeric Na+ channel complexes is regulated by .gtoreq.2 processes in the developing rat forebrain. Activation of Na+ channel .alpha. subunit gene transcription and the subsequent increase in Na+ channel mRNA are responsible for the major increases in .alpha. subunit protein and functional Na+ channels in the neonatal brain. However, changes in .alpha. subunit mRNA abundance alone are not sufficient to explain the kinetics of .alpha. subunit protein accumulation. Kinetic anal. suggests a requirement for a developmentally regulated translational or posttranslational step in brain Na+ channel expression.

IT Gene and Genetic element, animal
RL: BIOL (Biological study)
(for **sodium channel** .alpha. **subunit**, transcription of, of forebrain in ontogeny)

IT Development, mammalian
(**sodium channel** .alpha. **subunit** expression in forebrain in)

IT Embryo
(**sodium channel** .alpha. **subunit** expression in forebrain of)

IT Brain, metabolism
(prosencephalon, **sodium channel** .alpha. **subunit** expression in, in ontogeny)

IT Ion **channel**
(**sodium**, .alpha. **subunit**, expression of, in forebrain in ontogeny)

IT Proteins, specific or class
RL: BIOL (Biological study)
(**sodium channel**-forming, .alpha. **subunit**, expression of, in forebrain in ontogeny)

IT Ribonucleic acids, messenger
RL: BIOL (Biological study)
(**sodium channel**-forming protein-specifying, .alpha. **subunit**, of forebrain in ontogeny)

IT Synapse
(synaptosome, **sodium channel** .alpha. **subunit** of, of forebrain in ontogeny)

IT 7440-23-5, **Sodium**, biological studies
RL: BIOL (Biological study)
(**channel** for, .alpha. **subunit** of, expression of, in forebrain in ontogeny)

L12 ANSWER 38 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI .beta.2 **Subunits** of **sodium channels** from vertebrate brain. Studies with **subunit**-specific antibodies

AB The Na channel purified from rat brain is composed of 3 subunits: .alpha. [mol. wt. (Mr) 260,000], .beta.1 (Mr 36,000), and .beta.2 (Mr 33,000)]. The .alpha. and .beta.2 subunits are linked through **SS** bonds. Procedures are described for preparative isolation of the .beta.1 and .beta.2 subunits under native conditions. Pure .beta.2 subunits obtained by this procedure were used to prep. a specific anti-.beta.2 subunit antiserum. Antibodies purified from this serum by antigen affinity chromatog. recognized only **SS**-linked .alpha..beta.2 complexes and .beta.2 subunits in immunoblots, and immunopptd. 32P-labeled .alpha.

subunits of purified Na channels having intact **SS** bonds, but not those of Na channels from which .beta.2 subunits were detached by redn. of **SS** bonds. These antibodies also immunopptd. 89% of the high-affinity saxitoxin-binding sites from rat brain membranes, indicating that nearly all Na channels in rat brain have **SS**-linked .alpha..beta.2 subunits. Approx. 22% of .beta.2 subunits in adult rat brain are not **SS**-linked to .alpha. subunits. Anti-.beta.2 subunit antibodies are specific for Na channels in the central nervous system and do not cross-react with Na channels in skeletal muscle or sciatic nerve. The brains of a broad range of vertebrate species, including elec. eel, are shown to express Na channels with **SS** -linked .alpha..beta.2 subunits.

ST **sodium channel subunit** vertebrate brain; antibody **sodium channel subunit** vertebrate brain; disulfide **sodium channel subunit** vertebrate brain

IT Brain, composition
(**sodium channel** of, purifn. and interactions of **subunits** of, of vertebrate)

IT Antibodies
RL: BIOL (Biological study)
(to **sodium channel** .beta.2 **subunit** of rat brain, purifn. and specificity of)

IT Nervous system
(central, **sodium channels** of, of vertebrates, disulfide-bonded **subunits** of, immunol. study of)

IT 7440-23-5, **Sodium**, biological studies
RL: BIOL (Biological study)
(**channel** for, of vertebrate brain, purifn. and interactions of **subunits** of)

L12 ANSWER 39 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Palmitylation, sulfation, and glycosylation of the .alpha. **subunit** of the **sodium channel**. Role of post-translational modifications in channel assembly

AB Antibodies to the .alpha. and .beta.2 subunits and site-directed antibodies that distinguish .alpha. subunits of the RI and RII subtypes were used to study the biosynthesis and assembly of Na+ channels. The RII Na+ channel subtype is preferentially expressed in rat brain neurons in primary cell culture. Posttranslational processing of .alpha. subunits includes incorporation of palmityl residues in thioester linkage and sulfate residues attached to oligosaccharides. The incorporation of [3H]palmitate into .alpha. subunits is inhibited by tunicamycin, indicating that it occurs in the early stages of biosynthesis but after cotranslational glycosylation. Mature .alpha. subunits are attached to .beta.2 subunits through **SS** bonds within 1 h after synthesis and .ltoreq.30% can be specifically immunopptd. from the cell surface with antibodies against the .beta.2 subunits by 4 h after synthesis. The remaining .alpha. subunits synthesized in the presence of castanospermine and swainsonine have reduced apparent size. Castanospermine prevents incorporation of .apprx.81% of the sialic acid of the .alpha. subunit and inhibits sulfation but not palmitylation. Although inhibition of glycosylation with tunicamycin blocks assembly of functional Na+ channels, castanospermine and swainsonine do not prevent the covalent assembly of .alpha. and .beta.2 subunits or the transport of .alpha..beta.2 complexes to the cell surface, and Na+ channels synthesized under these conditions have normal affinity for saxitoxin. Thus, the extensive processing and terminal sialylation of oligosaccharide chains during maturation of the .alpha. subunit is not essential. A kinetic model for biosynthesis, processing, and assembly of Na+ channel subunits is presented.

ST **sodium channel** processing **subunit** assembly brain; palmitoylation **sodium channel** alpha **subunit** brain; sulfation **sodium channel** alpha **subunit** brain; glycosylation **sodium channel**

alpha **subunit** brain

IT Glycosidation
Sulfation
(of **sodium channel** .alpha.-**subunit** of
brain, **subunit** assembly in relation to)

IT Oligosaccharides
RL: BIOL (Biological study)
(processing of, of **sodium channel** .alpha.-
subunit of brain, **subunit** assembly relation to)

IT Acylation
(hexadecanoylation, of **sodium channel** .alpha.-
subunit of brain, **subunit** assembly in relation to)

L12 ANSWER 40 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AB Na+ crosses the apical membrane of tight epithelia through a Na+ channel, which is inhibited by the diuretic amiloride and by analogs such as phenamil (I). Target size anal. indicated that the functional size of the [3H]I binding sites assocd. with the epithelial Na+ channel from pig kidney is 90 kilodaltons (kDa). The [3H]I receptor was solubilized by using 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate. The solubilized material displayed the same properties of interaction with amiloride and its derivs. as did the membrane-bound receptor. A 2-step purifn. of the epithelial Na+ channel was achieved by using QAE Sephadex chromatog. and affinity chromatog. on a Bandeiraea simplicifolia lectin column. It resulted in a 1100-fold purifn. of the Na+ channel as compared to pig kidney microsomes with a yield of 15%. The maximal specific activity was 3.7 nmol/mg protein. SDS/PAGE of the purified Na+ channel under nonreducing conditions showed the presence of a single major polypeptide chain of apparent mol. mass 185 kDa. Under **SS** -reducing conditions, the purified epithelial Na+ channel migrated as a single band of apparent mol. mass 105 kDa. Hence, the epithelial Na+ channel from pig kidney has a total mol. mass of 185 kDa and consists of 2 nearly identical 90-105-kDa polypeptide chains crosslinked by **SS** bridges.

IT Cell membrane
(apical, **sodium channel** of, of kidney cortex,
purifn. and **subunit** structure of)

IT Kidney, composition
(cortex, **sodium channel** of apical membrane of,
purifn. and **subunit** structure of)

IT Ion **channel**
(**sodium**, of kidney apical membrane, purifn. and
subunit structure of)

IT 7440-23-5, **Sodium**, biological studies
RL: BIOL (Biological study)
(**channel** for, of kidney apical membrane, purifn. and
subunit structure of)

L12 ANSWER 41 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI Hydrophobic properties of the .beta.1 and .beta.2 **subunits** of the rat brain **sodium channel**

AB Voltage-sensitive Na+ channels purified from rat brain in functional form consist of a stoichiometric complex of 3 glycoprotein subunits, .alpha. [260 kilodaltons (kDa)], .beta.1 (36 kDa), and .beta.2 (33 kDa). The .alpha. and .beta.2 subunits are linked by **SS** bonds. The hydrophobic properties of these 3 subunits were examd. by covalent labeling with the photoreactive hydrophobic probe 3-(trifluoromethyl)-3-(m-[125I]iodophenyl)diazirine ([125I]TID) which labels transmembrane segments in integral membrane proteins. All 3 subunits of the Na+ channel were labeled by [125I]TID when the purified protein was solubilized in mixed micelles of Triton X-100 and phosphatidylcholine (4:1). The half-time for photolabeling was .apprx.7 min, consistent with the half-time of 9 min for photolysis of TID under these conditions. Comparable amts. of TID per mg of protein were incorporated into each subunit. Purified Na+ channels

reconstituted in phosphatidylcholine vesicles were also labeled by TID with comparable incorporation per mg of protein into all 3 subunits. The efficiency of photolabeling of the 3 subunits was reduced 39-44% by a 2-fold expansion of the hydrophobic phase of the reaction mixt. but was unaffected by a 2-fold expansion of the aq. phase, confirming that the photolabeling reaction took place in the lipid phase of the vesicle bilayer. The hydrophobic properties of the Na+ channel subunits were examd. further using phase sepn. in the nonionic detergent Triton X-114. Under conditions in which .beta.1 is dissocd. from .alpha., the .beta.1 subunit was preferentially extd. into the Triton X-114 phase, and the **SS**-linked .alpha..beta.2 complex was retained in the aq. phase. When the **SS** bonds between the .alpha. and .beta.2 subunits were reduced with dithioerythritol, the .beta.2 subunit was also preferentially extd. into the Triton X-114 phase leaving the free .alpha. subunit in the aq. phase. A preparative method for isolation of the .beta.1 and .beta.2 subunits was developed based on this technique. Considered together, the results of hydrophobic labeling and phase sepn. expts. indicate that the .alpha., .beta.1, and .beta.2 subunits all have substantial hydrophobic domains that may interact with the hydrocarbon domains with the hydrocarbon phase of phospholipid bilayer membranes. Since the .alpha. subunit is known to be a transmembrane protein with many potential membrane-spanning segments, it is concluded that the .beta.1 and .beta.2 subunits are likely to also be integral membrane proteins with .gtoreq.1 membrane-spanning segments. The specific extn. of these polypeptides into the detergent-rich phase in the phase sepn. expts. is discussed in terms of the possible distribution of the hydrophobic and hydrophilic domains of these subunits.

ST brain **sodium channel subunit** membrane segment; hydrophobicity **sodium channel subunit** brain

IT Phosphatidylcholines, biological studies
RL: BIOL (Biological study)
(membranes and micelles contg., voltage-sensitive **sodium channel subunits** .beta.1 and .beta.2 of brain interaction with, hydrophobic properties in relation to)

IT Phospholipids, biological studies
RL: BIOL (Biological study)
(membranes, voltage-sensitive **sodium channel subunits** .beta.1 and .beta.2 of brain spanning, hydrophobic properties in relation to)

IT Brain, composition
(voltage-sensitive **sodium channels** of, hydrophobic properties of .beta.1 and .beta.2 **subunits** of)

IT Membrane, biological
(bilayer, phospholipid, voltage-sensitive **sodium channel subunits** .beta.1 and .beta.2 of brain spanning, hydrophobic properties in relation to)

L12 ANSWER 42 OF 67 CAPLUS

TI Functional properties of rat brain **sodium channels** lacking the .beta.1 or .beta.2 **subunit**

AB The Na channel purified from rat brain is a heterotrimeric complex of .alpha. [mol. wt. (Mr) 260,000], .beta.1 (Mr 36,000), and .beta.2 (Mr 33,000) subunits. The .alpha. and .beta.2 are attached by **SS** bonds. Removal of .beta.1 subunits by incubation in 1.0M MgCl2 followed by reconstitution into phospholipid vesicles yielded a prepn. of .alpha..beta.2 which did not bind [3H]saxitoxin, mediate veratridine-activated 22Na+ influx, or bind the 125I-labeled .alpha.-scorpion toxin from Leiurus quinquestriatus (LqTx). In contrast, removal of .beta.2 subunits by redn. of **SS** bonds with 1.5 mM dithiothreitol followed by reconstitution into phospholipid vesicles yielded a prepn. of .alpha..beta.1 that retained full Na channel function. The .alpha..beta.1 bound [3H]saxitoxin with an dissocn. const. (KD) of 4.1 nM at 36.degree.. It mediated veratridine-activated 22Na+ influx at a

comparable initial rate as intact Na channels with a K0.5 for veratridine of 46 .mu.M. Tetracaine and tetrodotoxin blocked 22Na+ influx. Like intact Na channels, .alpha..beta.1 bound [125I]LqTx in a voltage-dependent manner with a KD of .apprx.6 nM at a membrane potential of -60 mV and was specifically covalently labeled by azidonitrobenzoyl [125I]LqTx. When incorporated into planar phospholipid bilayers, .alpha..beta.1 formed batrachotoxin-activated Na channels of 24 pS whose voltage-dependent activation was characterized by V50 = -110 mV and an apparent gating charge of 3.3. Thus, .beta.2 subunits apparently are not required for the function of purified and reconstituted Na channels, whereas a complex of .alpha. and .beta.1 subunits is both necessary and sufficient for channel function in the purified state.

ST **sodium channel subunit** function brain

IT Molecular association
(of **sodium channel** modulators with .beta.2 **subunit**-deficient brain **sodium channel**)

IT Brain, composition
(**sodium channel** of, **subunit** function in)

IT Biological transport
(**channel**-mediated, of **sodium**, brain **channel subunit** functions in)

IT Electric activity
(current-potential relationship, of **sodium channel** of brain deficient in .beta.2 **subunit**, in liposome)

IT Ion **channel**
(**sodium**, of brain, **subunits** of, function of)

IT Toxins
RL: BIOL (Biological study)
(.alpha.-, of scorpion, **sodium channel** of brain binding by, identification of channel functional **subunits** in)

IT 71-62-5, Veratridine 35523-89-8, Saxitoxin
RL: BIOL (Biological study)
(**sodium channel** of brain binding by, identification of functional **subunits** in)

L12 ANSWER 43 OF 67 CAPLUS

TI Biosynthesis and processing of the .alpha. **subunit** of the voltage-sensitive **sodium channel** in rat brain neurons

AB The Na channel from rat brain is a complex of .alpha. [260 kilodalton (kd)], .beta.1 (36 kd), and .beta.2 (33 kd) subunits. The .alpha. and .beta.2 subunits are linked by **SS** bonds. The earliest biosynthetic precursor of the .alpha. subunit is a 203-kd core polypeptide with sufficient high-mannose carbohydrate chains to increase its apparent size to 224 kd. It is processed to 224-kd and 249-kd precursor forms contg. complex carbohydrate chains before it achieves the mature size of 260 kd. Most newly synthesized .alpha. subunits are not **SS**-linked to .beta.2 subunits, but remain as a metabolically stable pool of intracellular subunits. The .alpha. subunits **SS**-linked to .beta.2 are found preferentially at the cell surface. A possible role for this intracellular pool as a rate-limiting step in the regulation of the cell surface d. and localization of Na channels in developing neurons is proposed.

ST **sodium** transport **channel subunit** brain;
disulfide sodium transport channel brain

IT Disulfide group
(of **sodium** transport **channel** .alpha. **subunit**, of nerve of brain)

IT Biological transport
(**channel**-mediated, of **sodium** by nerve of brain, formation and processing of .alpha. **subunit** of channel for)

L12 ANSWER 44 OF 67 CAPLUS

TI The **sodium channel** from rat brain. Separation and characterization of **subunits**

AB Procedures are described for sepn. of the .alpha., .beta.1, and .beta.2 subunits of the voltage-sensitive Na channel from rat brain by gel filtration in SDS before and after redn. of intersubunit **SS** bonds or by preparative SDS-gel electrophoresis. Partial proteolytic maps of the SDS-denatured subunits indicated that they are not identical polypeptides. The subunits are all heavily glycosylated and contain complex carbohydrate chains that bind wheat germ agglutinin. The apparent mol. wts. (Mr) of the sepd. subunits were estd. by gradient SDS-gel electrophoresis, by Ferguson anal. of migration in SDS gels of fixed acrylamide concn., or by gel filtration in SDS or guanidine hydrochloride. For the .alpha. subunit, SDS-gel electrophoresis under various conditions indicated an av. Mr of 260,000, whereas gel filtration methods gave anomalously low values. Removal of carbohydrate by sequential treatment with neuraminidase and endoglycosidase F resulted in a sharp protein band with apparent Mr = 220,000, suggesting that 15% of the mass of the native .alpha. subunit is carbohydrate. Electrophoretic and gel filtration methods yielded consistent Mr ests. for the .beta. subunits; the av. values are 36,000 and 33,000 for .beta.1 and .beta.2, resp. Deglycosylation by treatment with endoglycosidase F, trifluoromethanesulfonic acid, or HF produced sharp protein bands with apparent Mr = 23,000 and 21,000 for the .beta.1 and .beta.2 subunits, resp., suggesting that 36% of the mass of the native .beta.1 and .beta.2 subunits is carbohydrate.

ST **sodium channel** protein **subunit** brain;
glycoprotein sodium channel brain

IT Brain, composition
(**sodium-channel** glycoproteins of, purifn. and characterization of **subunits** of)

L12 ANSWER 45 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

TI A large intracellular pool of inactive **sodium channel** .alpha. **subunits** in developing rat brain

AB An intracellular pool of Na+ channel .alpha. subunits is detected in developing brain cells in vivo and in vitro by phosphorylation with cAMP-dependent protein kinase, immunopptn. with specific antiserum, and SDS gel electrophoresis or by RIA. These .alpha. subunits are membrane bound, contain complex carbohydrate chains, and have an apparent mol. wt. of 260,000 like mature .alpha. subunits. In contrast to mature .alpha. subunits, the intracellular subunits are not covalently attached to a .beta.2 subunit and do not bind saxitoxin with high affinity. They comprise 67-77% of the total immunoreactive .alpha. subunit in developing rat brain cells but are not a prominent component in the adult brain. This intracellular pool of .alpha. subunits may form a ready reserve of preformed subunits for incorporation into the surface membrane during periods of active membrane biogenesis. **SS** linkage of the .alpha. and .beta.2 subunits, insertion into the cell surface membrane, and attainment of a functional conformation appear to be closely related late events in the biogenesis of the Na+ channel. These processes may regulate the no. of functional Na+ channels in the developing brain.

ST **sodium channel subunit** brain development

IT Development, mammalian
(**sodium channel** inactive .alpha.-**subunits** of brain in)

IT Brain, composition
(**sodium channel** inactive .alpha.-**subunits** of, in development)

L12 ANSWER 46 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AB The gene for the beta-**subunit** of the epithelial **sodium channel** (betaENaC) is one of the most prominent candidate genes being analyzed for an association with human essential hypertension. It is known that a deletion or alteration of PY motif in exon 12 of betaENaC is responsible for Liddle's syndrome. Although the localization of genetic polymorphisms of betaENaC is unique to each

population, intensive analysis of individuals of white and African ancestry has demonstrated that genetic variants are localized in exons 8 and 12, with two frequent polymorphisms, G442V in exon 8 and T594M in exon 12. These two mutations are both found in individuals of African ancestry, and might be associated with elevated blood pressure (BP). Previously, we have screened the last two-thirds of exon 12 in the Japanese population, and demonstrated the absence of the T594M mutation and the presence of a novel P592S mutation. In the present study, we further examined the rest of exon 12 and exon 8 in a general population from. Ohasama, Japan (the Ohasama Study), using single-strand conformational polymorphism (**SSCP**) analysis. We screened 803 subjects randomly selected from the representative participants, who measured their home and casual BP. The PCR products presenting a shift in **SSCP** gels, as well as controls, were directly sequenced by autoanalyzer to identify the mutation. A novel gel shift was noted in exon 12 (n = 8) and sequencing identified a polymorphism at codon Ser 520, leading to no change in amino acid sequence (G77576C TCG-->TCC). In exon 8, all three **SSCP** variants were heterogynous for V434M (GTG-->ATG), which is coincident with a rare polymorphism in whites. The G442V mutation, however, was absent from the Japanese population. A novel mutation of exon 12 was not associated with a significant difference in clinical features. These results indicate that Japanese people possess three polymorphisms in exon 12, all of which are unique, and one in exon 8. These genetic variants of betaENaC may not influence the BP level of Japanese people. Am J Hypertens 2002;15:189-192 (C) 2002 American Journal of Hypertension, Ltd.

L12 ANSWER 47 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI T594M and G442V polymorphisms of the **sodium channel** beta **subunit** and hypertension in a black population
AB Polymorphisms of the epithelial sodium channel may raise blood pressure by increasing renal sodium reabsorption. This study examines frequency distributions and associations with hypertension of the T594M and of the G442V polymorphisms of the beta **subunit** of the epithelial **sodium channel** in a population-based sample. We studied a stratified random sample of 459 subjects (279 women), aged 40-59 years, of black African origin from general practices' lists within a defined area of South London. All were first generation immigrants. The polymorphic variants were detected using single strand conformational polymorphism technique (**SSCP**). The prevalence of hypertension (BP greater than or equal to 160 and/or 95 mm Hg or on drug therapy) was 43%; of these, 76% were on drug therapy. The main analysis was carried out by three ordered blood pressure categories (I to III) according to increasing blood pressure and presence or absence of drug therapy. The frequency of the 594M variant (heterozygotes and homozygotes) was 4.6%; the frequency of the 442V variant was higher (27.0%). The frequency of the 594M variant increased with increasing blood pressure category (P = 0.05) and was more common in hypertensives than normotensives. By contrast the frequency of the 442V variant did not vary across increasing blood pressure categories (P = 0.62). No gender difference was observed. Adjustment for age, sex and body mass index did not alter these findings. These results suggest that the 594M variant may contribute to high blood pressure in black people of African origin whereas the G442V polymorphism is unlikely to influence blood pressure in this population.

L12 ANSWER 48 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI Neuronal **sodium-channel** alpha 1-**subunit** mutations in generalized epilepsy with febrile seizures plus
AB Generalized epilepsy with febrile seizures plus (GEFS+) is a familial epilepsy syndrome characterized by the presence of febrile and afebrile seizures. The first gene, GEFS1, was mapped to chromosome 19q and was identified as the **sodium-channel** beta1-**subunit** , SCN1B. A second locus on chromosome 2q, GEFS2, was recently identified as the **sodium-channel** alpha1-**subunit**, SCN1A. Single-stranded conformation analysis (**SSCA**) of SCN1A was

performed in 53 unrelated index cases to estimate the frequency of mutations in patients with GEFS+. No mutations were found in 17 isolated cases of GEFS+. Three novel SCN1A mutations-D188V, V1353L, and I1656M-were found in 36 familial cases; of the remaining 33 families, 3 had mutations in SCN1B. On the basis of **SSCA**, the combined frequency of SCN1A and SCN1B mutations in familial cases of GEFS+ was found to be 17%.

L12 ANSWER 49 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI Study of the voltage-gated **sodium channel** beta 1 **subunit** gene (SCN1B) in the benign familial infantile convulsions syndrome (BFIC)
AB Benign familial infantile convulsions (BFIC) is a rare autosomal dominant epilepsy syndrome. This syndrome has been recently described in Italian and French pedigrees, Patients present with partial, then generalized seizures, with onset at age three months. The seizures usually spontaneously cease after one year without treatment, leaving no neurological abnormalities. We have mapped BFIC to chromosome 19q in five Italian pedigrees. The **sodium channel** beta 1 **subunit** gene (SCN1B) maps to this candidate region and has been shown to be involved in one Australian pedigree with generalized epilepsy and febrile seizures ''plus'' (GEFS +). In this family a missense mutation in SCN1B cosegregates with the GEFS+ phenotype. BFIC and GEFS+ have clinical features in common, therefore SCN1B is a candidate gene for BFIC, We studied SCN1B exons 1, 2, 3, 4, and 5, using four **SSCP** methods in 10 Caucasian BFIC probands of Western Europe. We found no exon variants. One variant was identified in intron 5 (IVS5-10C>G), which did not segregate with BFIC and was observed in 9.2% controls. A second variant in intron 5 was identified (IVS5 +30G>A). It was rare, as not observed in controls, but not segregating with the BFIC phenotype, Hum Mutat 16:139-142, 2000. (C) 2000 Wiley-Liss, Inc.
ST Author Keywords: benign familial infantile convulsions; BFIC; ICCA; infantile convulsions and choreoathetosis; voltage-gated **sodium channel** beta 1 **subunit** gene; SCN1B

L12 ANSWER 50 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI Japanese individuals do not harbor the T594M mutation but do have the P592S mutation in the C-terminus of the beta-**subunit** of the epithelial **sodium channel**: the Ohasama Study
AB Objective To assess the implications of polymorphisms of the amiloride-sensitive epithelial sodium channel in essential hypertension in the Japanese population by determining the incidence of the T594M mutation in the beta **subunit** of the epithelial **sodium channel**, and by screening the C-terminus of the epithelial sodium channel,

Methods Single-strand confirmational polymorphism (**SSCP**) analysis using two sets of primers which cover the last two-thirds of the last exon coding the B epithelial sodium channel and modification of a specific enzyme restriction site (N/aIII) for the T594M mutation were performed on 803 Japanese subjects. They were randomly selected from the study participants representative of a general population of Ohasama, Japan, who measured their home blood pressure. Polymerase chain reaction (PCR) products presenting a shift in **SSCP** gel, as well as controls, were directly sequenced by autoanalyser to identify the mutation.

Results **SSCP** analysis identified altered migration in five subjects. Four **SSCP** variants found by sequencing were heterogeneous for the P592S (CCT to TCT) mutation conserving the PY motif, although it was not significantly associated with either home or casual blood pressure values. The resting polymorphism was at codon Thr 594, leading to no change in the amino acid sequence (ACG to ACA). None of the PCR products were modified by N/aIII, indicating the absence of the T594M mutation.

Conclusions The epithelial sodium channel variants at the C-terminus are not involved in the common form of essential hypertension in Japanese.

J Hypertens 2000, 18:861-866 (C) Lippincott Williams & Wilkins.

L12 ANSWER 51 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI Identification of a novel human voltage-gated **sodium channel** alpha **subunit** gene, SCN12A
AB We have cloned a cDNA encoding a novel human voltage-gated **sodium channel** a **subunit** gene, SCN12A, from human brain. Two alternative splicing variants for SCN12A have been identified. The longest open reading frame of SCN12A encodes 1791 amino acid residues. The deduced amino acid sequence of SCN12A shows 37-73% similarity with various other mammalian sodium channels. The presence of a serine residue (S360) in the **SS2** segment of domain I suggests that SCN12A is resistant to tetrodotoxin (TTX), as in the cases of rat Scn10a (rPN3/SNS) and rat Scn11a (NaN/SNS2). SCN12A is expressed predominantly in olfactory bulb, hippocampus, cerebellar cortex, spinal cord, spleen, small intestine, and placenta. Although expression level could not be determined, SCN12A is also expressed in dorsal root ganglia (DRG), Both neurons and glial cells express SCN12A. SCN12A maps to human chromosome 3p23-p21.3, These results suggest that SCN12A is a tetrodotoxin-resistant (TTX-R) sodium channel expressed in the central nervous system and nonneural tissues, (C) 2000 Academic Press.

L12 ANSWER 52 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI Functional roles of the extracellular segments of the **sodium channel** alpha **subunit** in voltage-dependent gating and modulation by beta 1 subunits
AB Voltage-gated **sodium channels** consist of a pore-forming a **subunit** associated with beta 1 **subunits** and, for brain **sodium channels**, beta 2 **subunits**. Although much is known about the structure and function of the a subunit, there is little information on the functional role of the 16 extracellular loops. To search for potential functional activities of these extracellular segments, chimeras were studied in which an individual extracellular loop of the rat heart (rH1) alpha subunit was substituted for the corresponding segment of the rat brain type IIA (rIIA) alpha subunit. In comparison with rH1, wild-type rIIA alpha subunits are characterized by more positive voltage-dependent activation and inactivation, a more prominent slow gating mode, and a more substantial shift to the fast gating mode upon coexpression of beta 1 subunits in Xenopus oocytes. When a subunits were expressed alone, chimeras with substitutions from rH1 in five extracellular loops (IIS5-**SS1**, IISS2-S6, IIIS1-S2, IIISS2-S6, and TVS3-S4) had negatively shifted activation, and chimeras with substitutions in three of these (IISS2-S6, IIIS1-S2, and IVS3-S4) also had negatively shifted steady-state inactivation. rIIA alpha subunit chimeras with substitutions from rH1 in five extracellular loops (IS5-**SS1**, ISS2-S6, IISS2-S6, IIIS1-S2, and IVS3-S4) favored the fast gating mode. Like wild-type rIIA alpha subunits, all of the chimeric rIIA alpha subunits except chimera IVSS2-S6 were shifted almost entirely to the fast gating mode when coexpressed with beta 1 subunits. In contrast, substitution of extracellular loop IVSS2-S6 substantially reduced the effectiveness of beta 1 subunits in shifting rIIA. alpha subunits to the fast gating mode. Our results show that multiple extracellular loops influence voltage dependent activation and inactivation and gating mode of sodium channels, whereas segment IVSS2-S6 plays a dominant role in modulation of gating by beta 1 **subunits** . Evidently, several extracellular loops are important determinants of **sodium channel** gating and modulation.

L12 ANSWER 53 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AB Objective To investigate whether mutations in the C-terminus of the three **subunits** of the rat epithelial **sodium channel** (alpha beta gamma-rENaC) contribute to the hypertensive phenotype in five rat models for essential hypertension.
Design We sequenced the C-terminal regions of alpha-, beta- and

gamma-rENaC genes in five different hypertensive rat strains [spontaneously hypertensive rats (SHR), Dahl salt-sensitive (**SS** /Jr) rats, Milan hypertensive (MHS) rats, Sabra hypertensive (SBH) rats and Lyon hypertensive rats (LHR)] and their normotensive controls [Wistar-Kyoto (WKY) rats, Dahl salt-resistant (SR/Jr) rats, Milan normotensive (MNS) rats, Sabra normotensive (SBN) rats and Lyon normotensive rats (LNR)], Identified polymorphisms were tested for cosegregation with blood pressure as well as for increased epithelial sodium channel (ENaC) activity.

Methods Genomic DNA extracted from hypertensive and normotensive rat strains was amplified by the polymerase chain reaction and polymerase chain reaction fragments were sequenced. Cosegregation analysis was performed to test for correlations between blood pressure and different genotypes, The effects of a polymorphism on ENaC activity were assessed by functional expression in Xenopus laevis oocytes. The chromosomal location of the gene for gamma-ENaC was determined by linkage analysis in an F2 (MHS x MNS) population.

Results We found no polymorphisms at the C-terminus of alpha- and beta-rENaC in the five rat models tested, We identified two polymorphisms at the C-terminus of the gamma-subunit, one leading to an amino acid change, Milan strains (MNS and MHS) were polymorphic for this mutation. By cosegregation analysis we could exclude the possibility that there was a correlation between blood pressure and this polymorphism, Functional expression of the polymorphism caused no increase in ENaC activity assessed by measurement of the amiloride-sensitive sodium current in Xenopus oocytes, The gene for the gamma-ENAC was located on rat chromosome 1.

Conclusions No polymorphisms at the C-terminus of the three **subunits** of the epithelial **sodium channel** cosegregating with blood pressure were detected in five different genetic rat models for hypertension, If an altered ENaC activity contributes to the pathogenesis of hypertension in these rats, it must thus arise from mutations in other parts of the protein, from mutations outside the coding region impairing the proper regulation of one of the subunits or from mutations in an ENaC-associated protein. (C) Rapid Science Publishers.

L12 ANSWER 54 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Identification of amino acid residues in the alpha, beta, and gamma **subunits** of the epithelial **sodium channel** (ENaC) involved in amiloride block and ion permeation

AB The amiloride-sensitive epithelial Na channel (ENaC) is a heteromultimeric channel made of three alpha beta gamma subunits. The structures involved in the ion permeation pathway have only been partially identified, and the respective contributions of each subunit in the formation of the conduction pore has not pet been established. Using a site-directed mutagenesis approach, we have identified in a **short segment** preceding the second membrane-spanning domain (the pre-M2 segment) amino acid residues involved in ion permeation and critical for channel block by amiloride. Cys substitutions of Gly residues in beta and gamma subunits at position beta G525 and gamma G537 increased the apparent inhibitory constant (K-i) for amiloride by >1,000-fold and decreased channel unitary current without affecting ion selectivity. The corresponding mutation S583 to C in the alpha subunit increased amiloride K-i by 20-fold, without changing channel conducting properties. Coexpression of these mutated alpha beta gamma subunits resulted in a nonconducting channel expressed at the cell surface. Finally, these Cys substitutions increased channel affinity for block by external Zn2+ ions, in particular the alpha S583C mutant showing a K-i for Zn2+ of 29 mu M. Mutations of residues alpha W582L or beta G522D also increased amiloride K-i, the later mutation generating a Ca2+ blocking site located 15% within the membrane electric field. These experiments provide strong evidence that alpha beta gamma ENaCs are pore-forming subunits involved in ion permeation through the channel. The pre-M2 segment of alpha beta gamma subunits may form a pore loop structure at the extracellular face of the

channel, where amiloride binds within the channel lumen. We propose that amiloride interacts with Na+ ions at an external Na+ binding site preventing ion permeation through the channel pore.

L12 ANSWER 55 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AB The single strand conformation polymorphism (**SSCP**) technique was used to screen genomic DNA of a family with myotonia aggravated by cold, potassium loading and suxamethonium, but without muscle weakness. An aberrant band was found in exon 24 of SCN4A, the gene encoding the adult skeletal muscle **sodium channel** alpha-**subunit**
. DNA sequencing led to the detection of a G-to-A transition of cDNA nucleotide 4765 predicting a substitution of methionine for valine at position 1589 of the protein sequence. This amino acid is located within transmembrane segment S6 of channel repeat IV close to the cytoplasmic surface, a region which is supposed to act as acceptor of the inactivation gate of the channel. Four lines of evidence indicate that this mutation causes the disease: (i) the transition was only found for affected family members; (ii) no mutations were found in all other SCN4A exons; (iii) the affected gene region is conserved among various species; and (iv) an increase in the number of non-inactivating sodium channels had been revealed in earlier electrophysiological studies on an excised muscle specimen from the index patient. In addition, the close-by occurring substitution of valine for methionine at position 1592 known to cause hyperkalemic periodic paralysis was deduced for six families with the myotonic, non-dystrophic form of this disease.

L12 ANSWER 56 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

TI Genetic polymorphisms in the beta-**subunit** of the epithelial **sodium channel** (.beta.ENaC) gene in the Japanese population.

AB Background. Mutations have been found only in exons 8 and 12 of the .beta.-**subunit** of the epithelial **sodium channel** (.beta.ENaC), but the presence of other mutations in the remaining exons remains to be determined in the Japanese population. New cases with the V434M mutation should be identified because the identified individuals have high plasma sodium concentration. Methods. Exons 1 to 7 and 9 to 11 were screened by using single-strand conformational polymorphism (**SSCP**) in 200 subjects (100 normotensive and 100 hypertensive) randomly selected from 1245 participants in a community-based cohort study (Ohasama study) in northern Japan. Results. Four novel mutations were detected in exons 5, 6, and 7, and one of them was the novel missense mutation, P369H in exon 6. Then extended investigation of this mutation, together with those of V434M and P592S, which were identified in our previous studies, was performed in 1245 subjects. The final frequency of these mutations was 1/1245 for P369H, 5/1245 for V434M, and 5/1245 for P592S. Although a significant association with hypertension was not achieved, 3 of the 5 subjects with V434M were diagnosed as hypertensive. Plasma sodium concentrations were significantly high and plasma renin activity tended to be low in subjects with V434M. The only subject with P369H showed slightly elevated diastolic pressure, but no other abnormal characteristics were noted in the subjects with P369H or P592S. Conclusions. Genetic polymorphisms of .beta.ENaC in the Japanese population were determined. Clinical features in those with the V434M mutation suggest the presence of physiological effects of this mutation on plasma sodium regulation.

L12 ANSWER 57 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

AB The gene for the .beta.-**subunit** of the epithelial **sodium channel** (.beta.ENaC) is one of the most prominent candidate genes being analyzed for an association with human essential hypertension. It is known that a deletion or alteration of PY motif in exon 12 of .beta.ENaC is responsible for Liddle's syndrome. Although the localization of genetic polymorphisms of .beta.ENaC is unique to each population, intensive analysis of individuals of white and African ancestry has demonstrated

that genetic variants are localized in exons 8 and 12, with two frequent polymorphisms, G442V in exon 8 and T594M in exon 12. These two mutations are both found in individuals of African ancestry, and might be associated with elevated blood pressure (BP). Previously, we have screened the last two-thirds of exon 12 in the Japanese population, and demonstrated the absence of the T594M mutation and the presence of a novel P592S mutation. In the present study, we further examined the rest of exon 12 and exon 8 in a general population from Ohasama, Japan (the Ohasama Study), using single-strand conformational polymorphism (**SSCP**) analysis. We screened 803 subjects randomly selected from the representative participants, who measured their home and casual BP. The PCR products presenting a shift in **SSCP** gels, as well as controls, were directly sequenced by autoanalyzer to identify the mutation. A novel gel shift was noted in exon 12 (n = 8) and sequencing identified a polymorphism at codon Ser 520, leading to no change in amino acid sequence (G77576C TCG.fwdarw.TCC). In exon 8, all three **SSCP** variants were heterogynous for V434M (GTG.fwdarw.ATG), which is coincident with a rare polymorphism in whites. The G442V mutation, however, was absent from the Japanese population. A novel mutation of exon 12 was not associated with a significant difference in clinical features. These results indicate that Japanese people possess three polymorphisms in exon 12, all of which are unique, and one in exon 8. These genetic variants of .beta.ENaC may not influence the BP level of Japanese people. .COPYRGT. 2002 American Journal of Hypertension, Ltd.

L12 ANSWER 58 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI T594M and G442V polymorphisms of the **sodium channel** .beta. **subunit** and hypertension in a black population.
AB Polymorphisms of the epithelial sodium channel may raise blood pressure by increasing renal sodium reabsorption. This study examines frequency distributions and associations with hypertension of the T594M and of the G442V polymorphisms of the .beta. **subunit** of the epithelial **sodium channel** in a population-based sample. We studied a stratified random sample of 459 subjects (279 women), aged 40-59 years, of black African origin from general practices' lists within a defined area of South London. All were first generation immigrants. The polymorphic variants were detected using single strand conformational polymorphism technique (**SSCP**). The prevalence of hypertension (BP .gtoreq. 160 and/or 95 mm Hg or on drug therapy) was 43%; of these, 76% were on drug therapy. The main analysis was carried out by three ordered blood pressure categories (I to III) according to increasing blood pressure and presence or absence of drug therapy. The frequency of the 594M variant (heterozygotes and homozygotes) was 4.6%; the frequency of the 442V variant was higher (27.0%). The frequency of the 594M variant increased with increasing blood pressure category (P = 0.05) and was more common in hypertensives than normotensives. By contrast the frequency of the 442V variant did not vary across increasing blood pressure categories (P = 0.62). No gender difference was observed. Adjustment for age, sex and body mass index did not alter these findings. These results suggest that the 594M variant may contribute to high blood pressure in black people of African origin whereas the G442V polymorphism is unlikely to influence blood pressure in this population.

L12 ANSWER 59 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI Neuronal **sodium-channel** .alpha.1-**subunit** mutations in generalized epilepsy with febrile seizures plus.
AB Generalized epilepsy with febrile seizures plus (GEFS+) is a familial epilepsy syndrome characterized by the presence of febrile and afebrile seizures. The first gene, GEFS1, was mapped to chromosome 19q and was identified as the **sodium-channel** .beta.1-**subunit**, SCN1B. A second locus on chromosome 2q, GEFS2, was recently identified as the **sodium-channel** .alpha.1-**subunit**, SCN1A. Single-stranded conformation analysis (**SSCA**) of SCN1A was performed in 53 unrelated index cases to

estimate the frequency of mutations in patients with GEFS+. No mutations were found in 17 isolated cases of GEFS+. Three novel SCN1A mutations - D188V, V1353L, and I1656M - were found in 36 familial cases; of the remaining 33 families, 3 had mutations in SCN1B. On the basis of **SSCA**, the combined frequency of SCN1A and SCN1B mutations in familial cases of GEFS+ was found to be 17%.

L12 ANSWER 60 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI Study of the voltage-gated **sodium channel** .beta.1 **subunit** gene (SCN1B) in the benign familial infantile convulsions syndrome (BFIC).
AB Benign familial infantile convulsions (BFIC) is a rare autosomal dominant epilepsy syndrome. This syndrome has been recently described in Italian and French pedigrees. Patients present with partial, then generalized seizures, with onset at age three months. The seizures usually spontaneously cease after one year without treatment, leaving no neurological abnormalities. We have mapped BFIC to chromosome 19q in five Italian pedigrees. The **sodium channel** .beta.1 **subunit** gene (SCN1B) maps to this candidate region and has been shown to be involved in one Australian pedigree with generalized epilepsy and febrile seizures 'plus' (GEFS +). In this family, a missense mutation in SCN1B cosegregates with the GEFS+ phenotype. BFIC and GEFS+ have clinical features in common, therefore SCN1B is a candidate gene for BFIC. We studied SCN1B exons 1, 2, 3, 4, and 5, using four **SSCP** methods in 10 Caucasian BFIC probands of Western Europe. We found no exon variants. One variant was identified in intron 5 (IVSS-10C>G), which did not segregate with BFIC and was observed in 9.2% controls. A second variant in intron 5 was identified (IVSS+30G>A). It was rare, as not observed in controls, but not segregating with the BFIC. (C) 2000 Wiley-Liss, Inc.

L12 ANSWER 61 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI Japanese individuals do not harbor the T594M mutation but do have the P592S mutation in the C-terminus of the .beta.-**subunit** of the epithelial **sodium channel**: The Ohasama Study.
AB Objective: To assess the implications of polymorphisms of the amiloride-sensitive epithelial sodium channel in essential hypertension in the Japanese population by determining the incidence of the T594M mutation in the .beta. **subunit** of the epithelial **sodium channel**, and by screening the C-terminus of the epithelial sodium channel. Methods: Single-strand confirmational polymorphism (**SSCP**) analysis using two sets of primers which cover the last two-thirds of the last exon coding the B epithelial sodium channel and modification of a specific enzyme restriction site (NlaIII) for the T594M mutation were performed on 803 Japanese subjects. They were randomly selected from the study participants representative of a general population of Ohasama, Japan, who measured their home blood pressure. Polymerase chain reaction (PCR) products presenting a shift in **SSCP** gel, as well as controls, were directly sequenced by autoanalyser to identify the mutation. Results: **SSCP** analysis identified altered migration in five subjects. Four **SSCP** variants found by sequencing were heterogeneous for the P592S (CCT to TCT) mutation conserving the PY motif, although it was not significantly associated with either home or casual blood pressure values. The resting polymorphism was at codon Thr 594, leading to no change in the amino acid sequence (ACG to ACA). None of the PCR products were modified by NlaIII, indicating the absence of the T594M mutation. Conclusions: The epithelial sodium channel variants at the C-terminus are not involved in the common form of essential hypertension in Japanese. (C) Lippincott Williams and Wilkins.

L12 ANSWER 62 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI Identification of a novel human voltage-gated **sodium channel** A **subunit** gene, SCN12A.
AB We have cloned a cDNA encoding a novel human voltage-gated **sodium**

channel A **subunit** gene, SCN12A, from human brain. Two alternative splicing variants for SCN12A have been identified. The longest open reading frame of SCN12A encodes 1791 amino acid residues. The deduced amino acid sequence of SCN12A shows 37-73 similarity with various other mammalian sodium channels. The presence of a serine residue (S360) in the **SS2** segment of domain I suggests that SCN12A is resistant to tetrodotoxin (TTX), as in the cases of rat Scn10A (rPN3/SNS) and rat Scn11a (NaN/SNS2). SCN12A is expressed predominantly in olfactory bulb, hippocampus, cerebellar cortex, spinal cord, spleen, small intestine, and placenta. Although expression level could not be determined, SCN12A is also expressed in dorsal root ganglia (DRG). Both neurons and glial cells express SCN12A. SCN12A maps to human chromosome 3p23-p21.3. These results suggest that SCN12A is a tetrodotoxin-resistant (TTX-R) sodium channel expressed in the central nervous system and nonneural tissues. (C) 2000 Academic Press.

L12 ANSWER 63 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

TI Functional roles of the extracellular segments of the **sodium channel** .alpha. **subunit** in voltage-dependent gating and modulation by .beta.1 subunits.

AB Voltage-gated **sodium channels** consist of a pore-forming .alpha. **subunit** associated with .beta.1 **subunits** and, for brain **sodium channels**, .beta.2 **subunits**. Although much is known about the structure and function of the .alpha. subunit, there is little information on the functional role of the 16 extracellular loops. To search for potential functional activities of these extracellular segments, chimeras were studied in which an individual extracellular loop of the rat heart (rH1) .alpha. subunit was substituted for the corresponding segment of the rat brain type IIA (rIIA) .alpha. subunit. In comparison with rH1, wild- type rIIA .alpha. subunits are characterized by more positive voltage-dependent activation and inactivation, a more prominent slow gating mode, and a more substantial shift to the fast gating mode upon coexpression of .beta.1 subunits in Xenopus oocytes. When .alpha. subunits were expressed alone, chimeras with substitutions from rH1 in five extracellular loops (IIS5-**SS1**, IISS2-S6, IIIS1-S2, IIISS2-S6, and IVS3-S4) had negatively shifted activation, and chimeras with substitutions in three of these (IISS2-S6, IIIS1-S2, and IVS3- S4) also had negatively shifted steady-state inactivation. rIIA .alpha. subunit chimeras with substitutions from rill in five extracellular loops (IS5-**SS1**, ISS2-S6, IISS2-S6, IIIS1-S2, and IVS3-S4) favored the fast gating mode. Like wild-type rIIA .alpha. subunits, all of the chimeric rIIA .alpha. subunits except chimera IVSS2-S6 were shifted almost entirely to the fast gating mode when coexpressed with .beta.1 subunits. In contrast, substitution of extracellular loop IVSS2-S6 substantially reduced the effectiveness of .beta.1 subunits in shifting rIIA .alpha. subunits to the fast gating mode. Our results show that multiple extracellular loops influence voltage-dependent activation and inactivation and gating mode of sodium channels, whereas segment IVSS2-S6 plays a dominant role in modulation of gating by .beta.1 **subunits**. Evidently, several extracellular loops are important determinants of **sodium channel** gating and modulation.

L12 ANSWER 64 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

TI The study of amiloride sensitive **sodium channel** .beta. **subunit** exon 12 gene mutation by PCR-**SSCR** in primary hypertension.

AB To investigate exon 12 of amiloride sensitive **sodium channel** (ASSC) .beta. **subunit** gene mutation in patients with primary hypertension, in 148 definite primary hypertension subjects, PCR-**SSCP** was used to screen and define the mutation. The results showed that there were **SSCP** change of ASSC .beta. subunit gene exon 12 in 3 cases. It is suggested that mutation of ASSC .beta. subunit gene exon 12 may be related to primary hypertension, and this gene

mutation may be one of the molecular mechanisms for some common forms of patients with primary hypertension.

L12 ANSWER 65 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

AB Objective. To investigate whether mutations in the C-terminus of the three **subunits** of the rat epithelial **sodium channel** (.alpha..beta..gamma.-rENaC) contribute to the hypertensive phenotype in five rat models for essential hypertension. Design. We sequenced the C-terminal regions of .alpha.-, .beta.- and .gamma.-rENaC genes in five different hypertensive rat strains [spontaneously hypertensive rats (SHR), Dahl salt-sensitive (**SS**/Jr) rats, Milan hypertensive (MHS) rats, Sabra hypertensive (SBH) rats and Lyon hypertensive rats (LHR)] and their normotensive controls [Wistar-Kyoto (WKY) rats, Dahl salt-resistant (SR/Jr) rats, Milan normotensive (MNS) rats, Sabra normotensive (SBN) rats and Lyon normotensive rats (LNR)]. Identified polymorphisms were tested for cosegregation with blood pressure as well as for increased epithelial sodium channel (ENaC) activity. Methods. Genomic DNA extracted from hypertensive and normotensive rat strains was amplified by the polymerase chain reaction and polymerase chain reaction fragments were sequenced. Cosegregation analysis was performed to test for correlations between blood pressure and different genotypes. The effects of a polymorphism on ENaC activity were assessed by functional expression in Xenopos laevis oocytes. The chromosomal location of the gene for .gamma.-ENaC was determined by linkage analysis in an F2 (MHS x MNS) population. Results. We found no polymorphisms at the C-terminus of .alpha.- and .beta.-rENaC in the five rat models tested. We identified two polymorphisms at the C-terminus of the .gamma.-subunit, one leading to an amino acid change. Milan strains (MNS and MHS) were polymorphic for this mutation, By cosegregation analysis we could exclude the possibility that there was a correlation between blood pressure and this polymorphism. Functional expression of the polymorphism caused no increase in ENaC activity assessed by measurement of the amiloride-sensitive sodium current in Xenopus oocytes. The gene for the .gamma.-ENAC was located on rat chromosome Conclusions No polymorphisms at the C-terminus of the three **subunits** of the epithelial **sodium channel** cosegregating with blood pressure were detected in five different genetic rat models for hypertension. If an altered ENaC activity contributes to the pathogenesis of hypertension in these rats, it must thus arise from mutations in other parts of the protein, from mutations outside the coding region impairing the proper regulation of one of the subunits or from mutations in an ENaC-associated protein.

L12 ANSWER 66 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

TI Identification of amino acid residues in the .alpha., .beta., and .gamma. **subunits** of the epithelial **sodium channel** (ENaC) involved in amiloride block and ion permeation.

AB The amiloride-sensitive epithelial Na channel (ENaC) is a heteromultimeric channel made of three .alpha..beta..gamma. subunits. The structures involved in the ion permeation pathway have only been partially identified, and the respective contributions of each subunit in the formation of the conduction pore has not yet been established. Using a site-directed mutagenesis approach, we have identified in a **short segment** preceding the second membrane-spanning domain (the pre-M2 segment) amino acid residues involved in ion permeation and critical for channel block by amiloride. Cys substitutions of Gly residues in .beta. and .gamma. subunits at position .beta.G525 and .gamma.G537 increased the apparent inhibitory constant (K(i)) for amiloride by >1,000-fold and decreased channel unitary current without affecting ion selectivity. The corresponding mutation S583 to C in the .alpha. subunit increased amiloride K(i) by 20-fold, without changing channel conducting properties. Coexpression of these mutated .alpha..beta..gamma. subunits resulted in a non-conducting channel expressed at the cell surface. Finally, these Cys substitutions increased channel affinity for block by external Zn2+ ions, in particular the .alpha.S583C mutant showing a K(i) for Zn2+ of 29 .mu.M.

Mutations of residues .alpha.W582L or .beta.G522D also increased amiloride K(i), the later mutation generating a Ca2+ blocking site located 15% within the membrane electric field. These experiments provide strong evidence that .alpha..beta..gamma. ENaCs are pore- forming subunits involved in ion permeation through the channel. The pre-M2 segment of .alpha..beta..gamma. subunits may form a pore loop structure at the extracellular face of the channel, where amiloride binds within the channel lumen. We propose that amiloride interacts with Na+ ions at an external Na+ binding site preventing ion permeation through the channel pore.

L12 ANSWER 67 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

AB The single strand conformation polymorphism (**SSCP**) technique was used to screen genomic DNA of a family with myotonia aggravated by cold, potassium loading and suxamethonium, but without muscle weakness. An aberrant band was found in exon 24 of SCN4A, the gene encoding the adult skeletal muscle **sodium channel** .alpha.-**subunit**
. DNA sequencing led to the detection of a G-to-A transition of cDNA nucleotide 4765 predicting a substitution of methionine for valine at position 1589 of the protein sequence. This amino acid is located within transmembrane segment S6 of channel repeat IV close to the cytoplasmic surface, a region which is supposed to act as acceptor of the inactivation gate of the channel. Four lines of evidence indicate that this mutation causes the disease: (i) the transition was only found for affected family members; (ii) no mutations were found in all other SCN4A exons; (iii) the affected gene region is conserved among various species; and (iv) an increase in the number of non-inactivating sodium channels had been revealed in earlier electrophysiological studies on an excised muscle specimen from the index patient. In addition, the close-by occurring substitution of valine for methionine at position 1592 known to cause hyperkalemic periodic paralysis was deduced for six families with the myotonic, non-dystrophic form of this disease.

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L1            900 FILE CAPLUS
L2            711 FILE SCISEARCH
L3            588 FILE EMBASE
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L4           2199 S SODIUM (2A) CHANNEL (10A) (SUBUNIT OR UNIT)
L5           1065 FILE CAPLUS
L6           1198 FILE SCISEARCH
L7           1288 FILE EMBASE
     TOTAL FOR ALL FILES
L8           3551 S L4 AND SS? OR (SHORT SEGMENT?)
L9             45 FILE CAPLUS
L10            10 FILE SCISEARCH
L11            12 FILE EMBASE
     TOTAL FOR ALL FILES
L12            67 S L4 AND (SS? OR (SHORT SEGMENT?))

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L# LIST L1-L12 HAS BEEN SAVED AS 'TOXINSS1/L'

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